1   FOOD AND DRUG ADMINISTRATION

2   CENTER FOR DRUG EVALUATION AND RESEARCH

3   ADVISORY COMMITTEE FOR CARDIOVASCULAR AND RENAL DRUGS

4

5   Discussion Of Supplemental New Drug Application (Snda)

6   20-850/S-025, Telmisartan Tablets, 80 Milligrams,

7   Boehringer Ingelheim Pharmaceuticals, Inc., for the

8   Proposed Indication of Reduction in the Risk of

9   Myocardial Infarction, Stroke, Death from

10   Cardiovascular Causes, or Hospitalization for

11   Congestive Heart Failure in Patients 55 Years or Older

12   Who Are at High Risk of Developing Major

13   Cardiovascular Events.

14

15

16

17   WEDNESDAY, JULY 29, 2009

18   8:00 a.m. to 4:15 p.m.

19

20   Hilton Washington, D.C./Silver Spring

21   8727 Colesville Road

22   Silver Spring, Maryland

1 **CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE**

2 **MEMBERS (Voting)**

3

4 Robert A. Harrington, M.D., F.A.C.C. (Chair)

5 Professor of Medicine, Division of Cardiology

6 Department of Medicine

7 Duke University Medical School

8 Duke Clinical Research Institute

9 2400 Pratt Street, NP 7007

10 Room 0311, Terrace Level

11 Durham, North Carolina 27705

12

13 Sanjay Kaul, M.D.

14 Director, Cardiovascular Diseases

15   Fellowship Training Program

16 Cedars-Sinai Heart Institute

17 Division of Cardiology, Room 5536 S. Tower

18 8700 Beverly Blvd

19 Los Angeles, California 90048

20

21

22

1   Mori J. Krantz, M.D., F.A.C.C.

2   Associate Professor

3   University of Colorado/Cardiology, Denver Health

4   Director, CV Prevention, & ECG Core Lab

5   Colorado Prevention Center

6   789 Sherman St. Suite 200

7   Denver, Colorado 80203

8

9   Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.

10   Critical Care Nephrology Consulting

11   10427 Mayfield Road

12   Chesterland, Ohio 44026

13

14   **(Non-Voting)**

15   Jonathan C. Fox, M.D., Ph.D., F.A.C.C.

16   (Industry Representative)

17   Vice President, Clinical Therapeutic Area

18   Cardiovascular and Gastrointestinal Diseases

19   AstraZeneca LP

20   PO Box 15437

21   Wilmington, Delaware 19850

22

1 **(Temporary Voting)**

2 <u>Ralph B. D'Agostino, Ph.D.</u>

3 Professor, Mathematics/Statistics

4 and Public Health

5 Boston University

6 111 Cummington Street

7 Boston, Massachusetts 02215

8

9 <u>David DeMets, Ph.D.</u>

10 University of Wisconsin

11 600 Highland Avenue

12 K6-446A Clinical Science Center

13 Madison, Wisconsin 53792

14

15 <u>Sidney M. Wolfe, M.D.</u>

16 Acting Consumer Representative)

17 Director Health Research Group of Public Citizen

18 1600 20th Street NW

19 Washington, District of Columbia 20009

20

21

22

1   P R O C E E D I N G S

2   -   -   -   -   -

3   DR. HARRINGTON: Good morning. Why don't we

4   go ahead and get started? My name is Bob Harrington.

5   I'm a cardiologist from Duke University. I'll be the

6   chair of today's meeting. I'm required to read an

7   opening statement, and then I'll ask the advisory

8   panel meetings to introduce themselves before I turn

9   it over to Elaine to address the conflict of interest

10   statement.

11   For topics such as those being discussed at

12   today's meeting, there are often a variety of

13   opinions, some of which are quite strongly held. Our

14   goal is that today's meeting will be a fair and open

15   forum for discussion of these issues and that

16   individuals can express their views without

17   interpretation. Thus, as a gentle reminder,

18   individuals will be allowed to speak into the record

19   only if recognized by the chair. We look forward to a

20   productive meeting.

21   In the spirit of the Federal Advisory

22   Committee Act and the Government in the Sunshine Act,

1 we ask that the advisory committee members take care

2 that their conversations about the topic at hand take

3 place in the open forum of the meeting. We're aware

4 that members of the media are anxious to speak with

5 the FDA about these proceedings. However, the FDA

6 will refrain from discussing the details of the

7 meeting with the media until its conclusion.

8   Also, the committee is reminded to please

9 refrain from discussing the meeting topic during

10 breaks or lunch. Thank you.

11   So why don't we start with introductions?

12 If you could just give your name, your institution or

13 affiliation and your area of expertise.

14   Dr. Fox?

15   DR. FOX: My name is Jonathan Fox. I'm a

16 cardiologist in clinical development with AstraZeneca,

17 and I'm the industry representative to the committee.

18   DR. KAUL: My name is Sanjay Kaul. I'm a

19 cardiologist at Cedars-Sinai Medical Center in Los

20 Angeles.

21   DR. PAGANINI: Emil Paganini, adult and

22 critical care nephrologist out of Chesterland, Ohio.

1   DR. DeMETS: David DeMets, statistician,

2 University of Wisconsin.

3   MS. FERGUSON: Elaine Ferguson, designated

4 federal official.

5   DR. WOLF: Sid Wolf, internist and the

6 director of the Health Research Group at Public

7 Citizen.

8   DR. KRANTZ: I'm Mori Krantz, cardiologist,

9 University of Colorado in Denver.

10   DR. D'AGOSTINO: Ralph D'Agostino,

11 statistician from Boston University.

12   DR. O'NEILL: Bob O'Neill, director of the

13 Office of Biostatistics in Cedar.

14   DR. STOCKBRIDGE: I'm Norman Stockbridge.

15 I'm the director of the Division of Cardiovascular and

16 Renal Products at FDA.

17   DR. TEMPLE: Bob Temple, Office of Drug

18 Evaluation I, director, at FDA.

19   MS. FERGUSON: The Food and Drug

20 Administration is convening today's meeting of the

21 cardiovascular and renal drugs advisory committee

22 under the authority of the Federal Advisory Committee

1   Act, FACA, of 1972. With the exception of the

2   industry representatives, all members and temporary

3   voting members of the committee are special government

4   employees, SGEs or regular federal employees from

5   other agencies and are subject to federal conflict of

6   interest laws and regulations.

7   The following information on the status of

8   this committee's compliance with federal ethics and

9   conflict of interest laws covered by, but not limited

10 to, those found at 18 USC Section 208 and Section 712

11 of the Federal Food, Drug and Cosmetics Act, FD&C Act,

12 is being provided pursuant in today's meeting and to

13 the public.

14   The FDA has determined that members and

15 temporary voting members of this committee are in

16 compliance with the federal ethics and conflict of

17 interest laws under 18 USC Section 208. Congress has

18 authorized FDA to grant waivers to special government

19 employees and to regular federal employees who have

20 potential financial conflicts when it is determined

21 that the agency's need for a particular individual's

22 service outweighs his or her potential financial

1   conflict of interest.

2   Under Section 712 of the FD&C Act, Congress

3   has authorized FDA to grant waivers to special

4   government employees and regular federal employees

5   with potential financial conflicts when necessary to

6   afford the committee essential expertise.

7   Related to the discussions of today's

8   meetings, members and temporary voting members of this

9   committee have been screened for potential financial

10   conflicts of interest of their own as well as those

11   imputed to them, including those of their spouses or

12   minor children and for purposes of 18 USC Section 208,

13   their employers. These interests may include

14   investments, consulting, expert witness testimony,

15   contracts, grants, CRADAS, teaching, speaking,

16   writing, patents and royalties and primary employment.

17   Today's agenda involves discussion of

18   Boehringer Ingelheim's supplemental new drug

19   application 20-850/S-205, telmisartan tablets, 80

20   milligrams for the proposed indication of reduction in

21   the risk of myocardial infarction, stroke, death from

22   cardiovascular causes or hospitalization from

1   congestive heart failure in patients 55 years or older

2   who are at risk of developing major cardiovascular

3   events.

4   This topic is a particular matter involving

5   specific parties. Based on the agenda for today's

6   meeting, all financial interests reported by the

7   committee members and temporary voting members, no

8   conflict of interest waivers have been issued in

9   connection with this meeting. To ensure transparency,

10   we encourage all standing committee members and

11   temporary voting members to disclose any public

12   statements that they have made concerning the product

13   at issue.

14   With respect to the FDA's invited industry

15   representatives, we would like to disclose that

16   Dr. Jonathan Fox is participating in this meeting as

17   the non-voting industry representative acting on

18   behalf of regulated industry. Dr. Fox's role at this

19   meeting is to represent industry in general and not

20   any particular company. Dr. Fox is employed by

21   AstraZeneca.

22   We would like to remind members and

1   temporary voting members that if the discussions

2   involve any other products or firms not already on the

3   agenda for which an FDA participant has personal or

4   imputed financial interest, the participants need to

5   exclude themselves from such involvement and their

6   exclusion will be noted for the record. FDA

7   encourages all other participants to advise the

8   committee of any financial relationships they may have

9   with any firms at issue.   And I would

10   like to recognize Sandy Walsh from the press office.

11   Sandy, if you're here?

12   Sandy will be here later on today, I

13   suppose. Okay. She stepped out for a moment, if the

14   press has any questions for her. Thank you.

15   DR. HARRINGTON: So I've been reminded that

16   at scientific meetings following the presentation of

17   one or more of these trials that I've commented

18   publicly on the trials, I have had no direct

19   involvement in the research, no financial involvement

20   in any of the research activities related to the

21   product. But it was felt best that I state for the

22   record that I have actually commented on the trials in

1   scientific venues.

2   DR. KAUL: Likewise, I have also commented

3   on the trial at the scientific meetings, and I have no

4   conflicts of interest or any relationship whatsoever

5   with the sponsor.

6   DR. HARRINGTON: So just a few housekeeping

7   rules as we think about the conduct of the day. We'll

8   open with opening statements from Dr. Stockbridge

9   trying to put into context for the panel what the FDA

10   hopes to get out of today's proceedings. We'll then

11   turn our attention to a series of presentations by the

12   sponsor, which will take about an hour and a half.

13   The panel will then have about a half hour or so to

14   ask questions of the sponsor. Given the relatively

15   small size of the panel today, I will assure everybody

16   that we'll have plenty of time I think to make sure

17   everybody's questions get answered.

18   After a break, we'll turn our attention to

19   presentations by the FDA. And again, the panel

20   members will have the opportunity to ask questions of

21   the FDA presenters. We'll break for lunch, and then

22   the entire afternoon will be devoted to either further

1   questions if the panel has further questions. And as

2   the questioning to the sponsor and to the FDA wraps

3   up, we'll then turn our attention to the prepared

4   questions from the FDA to the panel and walk through

5   those over the course of the afternoon.

6   So if there's no questions about the format,

7   I will turn it over to Dr. Stockbridge.

8   DR. STOCKBRIDGE: I think today's discussion

9   is going to be very interesting. There are three

10 placebo-controlled comparisons for you to consider.

11 And I supposed it's not too prejudicial to say if they

12 were highly persuasive, we wouldn't be sitting here.

13 On top of that, you have an active-controlled trial,

14 which has issues that seem to warrant adding some

15 additional statistical expertise to the panel for

16 discussion today. So reasonable to infer from that

17 that it's hard to make the case from that alone, too.

18   So to the mix of those, the panel may decide

19 they want to consider other aspects of what they know

20 about either this product or other products in the

21 same class. And at the end of the day, what I'm

22 interested in is understanding how the various panel

1   members synthesize the information from these various

2   sources, all of which sort of lean in the right

3   direction and come to some conclusion. I think that's

4   generally true. I'm much more interested in

5   understanding how people put these various pieces of

6   information together to formulate an opinion about

7   approvability than I am about the actual vote at the

8   end of the day.

9   So thank you.

10   DR. HARRINGTON: Thank you, Dr. Stockbridge.

11   Well, let's turn our attention now to the

12 sponsor's presentation. I think the panel members are

13 all experienced members and know that the general

14 format is we'll let the sponsor get through all their

15 presentations and then ask questions after all of

16 them. Of course, if you have a burning question that

17 really requires clarification, just notify me and

18 we'll see if we can stop along the way.

19   DR. VOIGT: Good morning, Mr. Chairman,

20 members of the committee, representatives of the FDA,

21 ladies and gentlemen. It's a pleasure to be here

22 today on behalf of Boehringer Ingelheim to discuss the

1   results of our telmisartan study program for

2   prevention of cardiovascular events.

3   I'm Thor Voigt, senior vice president of

4   Medicine and director of Regulatory affairs at

5   Boehringer Ingelheim. I will provide a brief

6   introduction at the beginning of today's

7   presentations.

8   Cardiovascular disease is a major health

9   concern for society inside and outside of the United

10 States. In the U.S., we have some 8 million patients

11 suffering from a myocardial infarction annually. We

12 have almost six and a half million patients suffering

13 from a stroke and, unfortunately, almost 900 patients

14 die. So I think there is almost no doubt that more

15 effective alternative treatments are needed to reduce

16 risks for those patients.

17   Important outcome studies were done in the

18 past and established that ACE inhibitors and ARBs are

19 effective treatments for the reduction of

20 cardiovascular events. You all know those studies,

21 SOLVD, SAFE, LIFE and HOPE. They changed treatment

22 guidelines. They were introduced into the clinical

1   practice. Then they answered very important question.

2   But they also raised new questions, and they raised

3   new hypotheses.

4   For example, are ARBs clinical comparable to

5   ACE inhibitors? Is dual RAAS blockade more effective

6   than single RAAS blockade? Are ARBs superior to

7   placebo in those patients who cannot tolerate ACE

8   inhibitors?

9   In order to help answer those questions and

10 to find out answers for those hypotheses, our academic

11 partners in Boehringer Ingelheim embarked on a study

12 program, the ONTARGET study program. The critical,

13 the pivotal trial was ONTARGET. This study was done

14 in 25,000 patients at 700 sites worldwide. And it

15 tested whether dual RAAS blockade is more effective

16 than single RAAS blockade by ramipril. And secondly,

17 is telmisartan clinically comparable to ramipril?

18   In this context, we also would like to

19 discuss with you two other studies in the sense of

20 supportive data. It's TRANSCEND. This study was done

21 in 6,000 patients in 600 sites worldwide. And this

22 tested whether telmisartan is effective in ACE

1   inhibitor intolerant patients.

2   Finally, PRoFESS, a study with 20,000

3   patients, a study for the secondary prevention of

4   stroke where we tested telmisartan and whether this is

5   superior to placebo.

6   Let me briefly lead you during today's

7   presentation. We slightly changed that when we saw

8   the questions from the agency. The next speaker will

9   be Professor James Young, executive dean, Cleveland

10   University. He will talk about the medical need. He

11   will be followed by Profession Salim Yusuf, McMaster

12   University, Hamilton, Ontario, Canada.

13   I want to say that Professor Yusuf was the

14   principal investigator for the ONTARGET and the

15   TRANSCEND study. Within his institution, the database

16   was held. Within his institution, the primary

17   analysis of the database was done before the database

18   was transferred to Boehringer Ingelheim.

19   Subsequently, we will have Dr. Jeff

20   Friedman. Jeff Friedman is the therapeutic head,

21   cardiovascular, at Boehringer Ingelheim, and he will

22   present the safety information about telmisartan with

1   specific focus on the program to be presented.

2   Finally, we will have Professor Young again

3   with the benefit risk judgment as well as our final

4   conclusions.

5   Professor Young?

6   DR. YOUNG: Thank you, Thor.

7   Dr. Harrington, panelists, FDA

8   representatives, colleagues, audience, good morning.

9   My name is Jim Young, and I am the executive dean of

10 the Cleveland Clinic Lerner College of Medicine,

11 chairman of the Endocrinology and Metabolism Institute

12 and also a cardiologist.

13   I was one of the United States co-principal

14 investigators for ONTARGET/TRANSCEND and to set the

15 stage, would like to share some of my thoughts

16 regarding the clinical considerations before the panel

17 today.

18   We all know well the burden of

19 cardiovascular disease Dr. Voigt reviewed. These data

20 from my perspective emphasize the prevalence of

21 cardiovascular disease, including hypertension, and

22 emphasize the extraordinary impact perhaps focused

1   most on the incidence of subsequent myocardial

2   infarction, stroke and heart failure. It is indeed

3   clinically problematic.

4   Juxtaposed to this major health concern is

5   the fact that we have limited choice of therapies

6   having cardiovascular risk reduction as an indication,

7   particularly, therapies that are reasonably well

8   tolerated and safe by our patients. Perhaps it is

9   sophomoric but still I think important to reflect on

10 that fact that when prescribing any drug, we should do

11 so in light of available evidence with the goal of

12 making a patient feel better, aspirin for headache,

13 curing a disease, penicillin for pneumococcal

14 pneumonia or preventing a morbid cardiovascular event,

15 ramipril in patients at risk.

16   From the patients' and clinicians'

17 perspective, it is important to have additional

18 effective treatment options for this indication to

19 provide an alternative to the ACE inhibitor ramipril.

20 And so we are here today to discuss the extensive

21 telmisartan database with respect to safety and

22 efficacy in comparison to the ACE inhibitor ramipril.

1   Indeed, there's an extraordinary depth and

2   breadth of clinical experience with this ARB. This

3   includes a well characterized post-marketing

4   experience in hypertensive patients of greater than 10

5   years with more than 19 million patient years of drug

6   exposure and a safety profile that is consistent with

7   other ARBs.

8   Additionally, the robust clinical trial

9   database contains high quality, randomized, controlled

10   international, multi-center data that defines safety

11   and expected outcomes. The total observation time for

12   patients in the CV risk reduction trials,

13   ONTARGET/TRANSCEND and PRoFESS, was about 180,000

14   patient years with more than 50,000 patients at high

15   risk for cardiovascular events.

16   We believe the data to be discussed today

17   supports the concept that telmisartan is a safe,

18   effective and attractive option for clinicians to use

19   to reduce the risk of morbid cardiovascular events in

20   select patients. This is important because though the

21   ACE inhibitor ramipril was found effective for this

22   and set the "gold standard", quote, unquote, many

1 patients have difficulties with ramipril due to side

2 effects.   Indeed, clinicians often use

3 an ARB because of a more attractive side effect

4 profile to achieve various therapeutic endpoints.

5 Patients and clinicians, I believe, would benefit by

6 having an alternative therapy to ramipril for broad

7 cardiovascular risk reduction. And the ONTARGET,

8 TRANSCEND and PRoFESS databases address this need.

9   Also, based on the clinical trial data in

10 evidence, we would like to point out and emphasize

11 that we are addressing the question of non-inferiority

12 of telmisartan compared to ramipril and not the

13 superiority of the combination of telmisartan and

14 ramipril. We don't advocate that particular approach.

15   Professor Salim Yusuf, well known to

16 everyone, principal investigator for the

17 ONTARGET/TRANSCEND efforts and a significant

18 participant in PRoFESS, will present the efficacy data

19 supporting the requested label expansion to be

20 considered today and also, importantly, reflect on the

21 trial design and outcome observations in the databases

22 that we are discussing.

 1   Salim?

 2   DR. YUSUF: Good morning, ladies and

 3 gentlemen. I want to start off by saying two things.

 4 One is I've been involved in clinical trials since

 5 1976, first working in Oxford trying to design large,

 6 simple trials and trying to make the field more

 7 reliable as well as in meta-analyses. So these are my

 8 academic interests, and I will speak from that

 9 perspective, not necessarily defending a trial, not

10 necessarily defending a sponsor's position.

11   Since Oxford, I had the good fortune of

12 working in the U.S. at NHLBI. And during these

13 periods, and then subsequently at McMaster, I've been

14 privileged to interact with some of the best clinical

15 trial minds in the world. Some of the things that I'm

16 going to discuss may sound like a little bit of a

17 tutorial. I beg your pardon for that, but these are

18 lessons I've learned at breakfast tables, airport

19 lounges and other things.

20   I also want to thank the FDA for something.

21 The FDA has been a mine for methodological

22 improvement, and FDA clinicians, statisticians have

 1   pushed us. But one of the things that I find is non-

 2   inferiority trials are amongst the hardest parts of

 3   clinical trials. And so standard methodology of pre-

 4   defining one endpoint, one P-value, probably needs to

 5   be broadened. And I think Dr. Stockbridge raised

 6   that. We have to look at the continuum of evidence,

 7   the totality of the data, the burden of disease. And

 8   that's what I'm going to focus on.

 9   So let's start with HOPE. I was privileged

10   to be the principal investigator and the designer of

11   the study. I have to curiously thank Bob Temple for

12   the study, and he doesn't know it or he may know it.

13   It started off at a rejection at the FDA panel when I

14   presented the SOLVD data, and despite the fact we had

15   a clear reduction in MI, the committee turned it down.

16   And Bob pulled me aside and said, "What do you want?

17   You got a reduction in mortality approved; why do you

18   want a reduction in MI?"

19   I was determined to prove that the reduction

20   in MI was real. Of course, I only had a one-sided

21   hypothesis. With a great deal of difficulty, we

22   raised money from 14 sources and did the HOPE trial.

1   And we did a trial of 9,000 people and people without

2   heart failure high risk, and we demonstrated that

3   ramipril versus placebo on top of standard therapy

4   clearly reduced cardiovascular death, myocardial

5   infarctions, stroke by about a fifth to a quarter,

6   highly significant.

7   It involved a broad group of high-risk

8   patients, not just coronary disease. But it also

9   included cerebral vascular disease, peripheral

10 vascular disease and high-risk diabetes. There's been

11 no other trial of ACE inhibitors versus placebo with

12 this breadth of patients in people without heart

13 failure.

14   The other thing to note, which I won't show

15 you, but it's published amply, is that the results

16 were consistent in various subgroups examined by risk

17 and by concomitant therapy. This meant the effects of

18 ramipril were consistent, at least if you translate it

19 into statistical terms, approximately constant across

20 all these different categories.

21   Lastly, the point that Jim pointed out, that

22 one-quarter of people stop ramipril because of

1   intolerance.

2   So these are the results overall. There's a

3   highly significant reduction in the primary endpoint

4   of cardiovascular death, MI and stroke, 18 percent

5   down to 14 percent, 22 percent reduction, fairly tight

6   confidence limits, highly significant results.

7   There are very few trials in the literature

8   that give you such robust answers. If you expand it

9   to include heart failure and hospitalizations, the

10   event rate goes up. The effect sizes are identical.

11   The confidence limits are slightly tighter.

12   Consistent effects on death, myocardial infarction,

13   stroke and a trend towards heart failure

14   hospitalizations, which we think was an underestimate

15   because when you look at the total heart failure, any

16   heart failure, .77 is the hazard ratio, which is

17   similar to this.

18   Now, when we designed the ONTARGET program,

19   we were aware of several factors. We were aware only

20   of the HOPE trial because no other trial in this field

21   had been completed. So we had to base our design on

22   the study.

1   The second is we realized that the field of

2   non-inferiority trials was evolving. And we knew that

3   there would be different perspectives, so we designed

4   a program as opposed to a trial. And the way we went

5   about it, it was really we wanted to find out whether

6   telmisartan reduced events. And in order to achieve

7   that, we used different approaches.

8   The first one was a non-inferiority design

9   aspect of it of telmisartan versus ramipril. The

10 second one was the superiority design, and this was

11 primarily a medical question. But on reflection in

12 the last 24 hours, it's also a statistical question.

13 And the medical question was, was combination dual

14 therapy superior to telmisartan, which is the

15 sponsor's question. To me, if these two are the same,

16 are these superior to either of these dual blockade

17 versus single blockade.

18   For at one minute you can actually -- for a

19 moment if you reflect, this addresses two mechanisms

20 of blocking or one mechanism. But if they're

21 equivalent, what this is addressing is dose response.

22 Are you hitting a flattening of the dose response? So

1   some degree of blockade of the renin-angiotensin

2   system was a small degree of blockade. And that's

3   probably just as important for the field generically

4   than rather one or two drugs.

5   The last thing was in those unable to

6   tolerate ACE inhibitors, what does telmisartan do? On

7   reflection, the fact that somebody doesn't tolerate an

8   ACE inhibitor is telling them they're different from

9   the people who entered HOPE. Really, there isn't

10 another trial in this population without heart

11 failure. And a priori, I don't know whether I would

12 expect for sure an identical result to HOPE or an

13 approximate result to HOPE.

14   So if I got exactly the same results, I'd be

15 brilliantly happy. If I got some result that is

16 within a reasonable clinical worthwhile benefit, well,

17 that's reasonable. And I would use all this

18 information in trying to understand what telmisartan

19 would do.

20   The sponsor had decided to do a study called

21 PRoFESS in strokes, post-ischemic strokes of two

22 anti-platelet agents. That was the original design,

1   Clopidigrel versus Aggrenox, a combination of aspirin

2   plus dipyridamole.

3   At an advanced stage in the design of the

4   study, I was invited by the co-chairs and the company

5   to be the third co-chair and bring in some

6   cardiological expertise. And I raised the issue, this

7   is an opportunity to study telmisartan because there

8   is an interesting question. And the interesting

9   question was what happens when you give telmisartan

10 early after a stroke. This is not long term after a

11 stroke but early after a stroke.

12   So in PRoFESS, the design was to start

13 treatment as early as possible but no later than 90

14 days. And 50 percent of the people entered within 10

15 days, and 50 percent of the events occurred within six

16 months. So PRoFESS is a mixture of early effects and

17 late effects. TRANSCEND and ONTARGET is largely the

18 result of long-term therapy.

19   So here is the ONTARGET design. And you'll

20 see this is one of the largest programs in the world,

21 35,000 people in secondary prevention. I may be

22 mistaken if I said this is the largest secondary

1 prevention trial in cardiovascular disease but

2 probably not. I know the Women's Health Initiative in

3 primary prevention is even larger.

4   You'll see we had a run-in phase in

5 ONTARGET. These are people who couldn't tolerant an

6 ACE inhibitor a priori. About 10 percent were

7 excluded here. If the reason they were excluded was

8 because of ACE intolerance, they could go here, but

9 fresh patients also came in here. And the original

10 design was about 7,000 people to each of the three

11 arms. We were able to recruit more people. And

12 eventually, we had a mean, longer follow-up because we

13 recruited six months faster. And so they were

14 followed for about five and a half years.

15   In TRANSCEND, we originally had 5,000

16 people. We were able to push it to 6,000. And so we

17 have 3,000 in each arm and again, a similar duration

18 of follow-up.

19   Now, I must say, 6,000 is substantially

20 lower than the HOPE study's 9,000. Now, focusing on

21 ONTARGET, we were going to test for superiority of

22 combination versus ramipril and for non-inferiority

1   between telmisartan and ramipril. And of course, the

2   design gives you a chance to test this versus this as

3   well.

4   Now, we tried very hard to have the same

5   entry criteria. But remember this is a trial three

6   times larger than HOPE, so we needed more countries,

7   more centers. And despite the fact it's similar entry

8   criteria, you end up with more or less the same

9   patients but some things change because of differences

10   in centers and differences in time. And you will see

11   that the percent of women and the age was similar.

12   That was easy to get the same. Coronary artery

13   disease, about the same, but peripheral artery

14   disease, there was much more at HOPE than in ONTARGET.

15   Strokes, TIAs, cerebral vascular disease was twice as

16   common in ONTARGET versus HOPE. Hypertension, more

17   common partly because it's definitional because the

18   threshold for hypertension is changing. And this

19   blood pressure, 140 by 82 or 139 by 79 is nominally

20   highly significant, but you've got to understand

21   there's a difference in measurement.

22   This was ordinary cuff clinic measurements

1   using whatever clinics use. This was standardized

2   measurement using an Omron cuff, and we've done

3   various studies where this over-reads this by about

4   2 millimeters. So this is essentially the same blood

5   pressure.

6   Statin use increased, but I must say that

7   during the conduct of HOPE, statin use went up from

8   30 percent of the beginning to 50 percent at the end.

9   Anti-platelet drugs were the same. Diuretics, much

10 more here. Calcium beta blockers, much more here.

11 And what I haven't plotted is calcium blockers, much

12 more here.

13   So we were doing ONTARGET against a

14 background of more regressive therapy. Now, the one

15 question you can ask is does this matter. And that's

16 something we can explore later, and I'll give you a

17 few examples.

18   Now, why did we use a different endpoint?

19 Well, we needed a larger study. And non-inferiority

20 trials require more people. And therefore, to

21 maintain power, had we used the ramipril triple

22 endpoint, we'd end up with a 14 percent event rate,

1   not the 18 percent event rate we saw in HOPE in the

2   control group. So by moving it here, we expected we

3   would see a higher event rate than if we observed the

4   4-fold endpoint. And note, we expected that the

5   effect sizes would be the same.

6   So therefore, this is the result of the

7   primary endpoint in HOPE, second endpoint if you do

8   the quadruple. This was reversed. Then this became

9   the secondary endpoint. This became this. But this

10 was the key secondary endpoint in ONTARGET. And it's

11 important to look at both of these collectively, one,

12 because they correlate closely, 18 percent of this is

13 included in this or the other way around. And so you

14 want to see consistency and coherence between the two

15 endpoints. They're not really two endpoints. It's

16 one and 1.2 endpoints. That's the way to think of it.

17   Now, this is the sponsor calculation of

18 non-inferiority margin. The hazard ratio of ramipril

19 over placebo was .775, what I showed you, .78. This

20 is the confidence interval. If you flip that around,

21 1 by .775, you get a hazard ratio of 1.29 of placebo

22 over ramipril and these are the confidence intervals.

1   Now, Boehringer Ingelheim used a hazard

2   ratio that was half a standard error below the point

3   estimate. That is 1.26 instead of 1.29. So there's

4   some discounting. Then we took 50 percent of the

5   accessories of the lower confidence interval and

6   that -- of the 1.26, not the confidence interval.

7   That is half. So a second step in discounting.

8   This is a method that was described in the

9   literature at that time, and I believe used in other

10   trials by Hasselblad and Kong. And it is somewhat

11   similar, not identical to the virtual comparison

12   method that was later published by Wang, Hung and

13   Tsong from the FDA in 2002.

14   So this is what was used by the sponsor, the

15   protocol specified approach. This approach was very

16   similar to what was used in another trial of an ARB,

17   which is the Valiant study. And indeed, it ended up

18   with the same margin. Of course, it was a different

19   endpoint because it was a slightly different

20   population from HOPE. But it's information in its

21   context, and I think this is the point Dr. Stockbridge

22   was getting to.

1   Now, the FDA did at the beginning want a

2   more stringent margin. I think it's important to

3   acknowledge that. Now, the recommendation was using

4   what is called the confidence interval method, which

5   is one-sided, 97.5 percent or two-sided, 95 percent.

6   This was the confidence interval, and they wanted 50

7   percent of that. So this discounts it, but to a

8   greater extent than what the protocol specified. And

9   this is discussed in detail, and it's called the ICIC

10   method proposed by Wang, Hung and Tsong in the same

11   article I related to.

12   So these are differences there. And the key

13   thing is not to focus on one or the other but on which

14   is right. Nobody can say which is right. This is

15   more conservative than this. This is conservative.

16   There is some discounting. This is even more

17   conservative.

18   Now, what are the results of ONTARGET?

19   First, the results are probably best expressed here.

20   We have three groups, telmisartan, ramipril,

21   telmisartan plus ramipril. Right from the beginning

22   to the end of the trial, the three curves are on top

1 of each other. There's no hint of wobble in any

2 direction.

3   Now, let's look at the combination therapy

4 versus ramipril. Eight and a half thousand patients

5 to each, 17,000, a lot of events. 1400 events versus

6 1400 events, dead even. Same for the -- that's a

7 quadruple endpoint. Look at the consistency with the

8 so-called secondary endpoint. 2400 events evenly

9 split. Consistency in each component and overall, a

10 hazard ratio of 1, tight confidence limits. And

11 that's a superiority p-value. Obviously, this is

12 obviously   non-significant.

13   This, while it's a disappointment to many

14 people, actually confirms what Valiant showed. It

15 actually shows -- as I go through, I'll point out the

16 similarities both in the design and the results of

17 Valiant and the ONTARGET program. So this sets to

18 rest an important concept in the field.

19   Now, what about the non-inferiority

20 comparison of telmisartan versus ramipril? And this

21 is the primary endpoint analysis. That's the

22 quadruple analysis; 1412 here, 1423, 28, 50 events and

1   yet, they're so similar to each other, formal

2   calculation, a hazard ratio, 1.01, confidence limits

3   .93 and 1.0. And compared to the protocol pre-

4   specified margin, that is highly significant. This is

5   a one-sided p-value, and that's what. And this is the

6   97.5. If you take the 95 percent confidence limits,

7   that inches down a little. But really, these two

8   hazard ratios and confidence limits are identical.

9   That's the way I read it. I don't split hairs on a p-

10 value or on a confidence interval.

11   Now, if you look at the p secondary

12 endpoint. it is pre-specified, again, about 1200

13 events each. You will see hazard ratio of 1. Highly,

14 top confidence limit's 1.08. And this is non-

15 inferiority P. It's telling you how far you are away

16 from the 1.13 margin. Again, it's .99. Again, 1.07,

17 1.08 is just below. Not only 1, it's well below the

18 1.13, but it's also well below the 1.085 that the FDA

19 had requested us to consider. And this obviously is

20 the same result.

21   Now, here are the data on the 4-fold

22 endpoint right on top of each other throughout, 3-fold

1   endpoints right on top of each other throughout. So

2   there's a consistency in the data throughout the

3   study, consistency across two endpoints and different

4   ways of analyzing it.

5   Now, this is the summary of this. This is

6   the hazard ratio 1 with a confidence interval. And

7   what this is the protocol specified non-inferiority

8   margin. This is the FDA pre-specified non-inferiority

9   margin. On the quadruple endpoint, you will see that

10 this is significantly lower than this but just crosses

11 that. On the triple endpoint, the upper confidence

12 limit crosses both.

13   I'll point out the one-sided p-value for

14 this is 0.03. Now, remember, one-sided should be

15 0.025. So it just sort of misses it. And this one,

16 the one sided, is 0.01, which is the equivalent of --

17 versus this margin. So if you're a p-valuer, this is

18 nominally significant, whatever method you use. This

19 is just short of being significant using the FDA

20 margin and clearly significant using the non-

21 inferiority margin.

22   Now, the other thing I wanted to show you

1 was there are two issues that we know that has changed

2 from HOPE. One is concomitant therapy. The other is,

3 despite our best efforts, we ended up with a lower

4 event rate than HOPE. And so we looked at the data by

5 the HOPE risk score and we found that in ONTARGET,

6 telmisartan versus ramipril, the results were

7 consistent independent of risk. So this is 10 percent

8 over 5 years or 2 percent per year. This is 25

9 percent over 5 years or 5 percent a year. So over a

10 two and a half-fold background risk, the results of

11 the trial were consistent.

12   So inherent risk doesn't seem to make much

13 of a difference, so constancy if you want to call it.

14 Statins, which is the main thing that increased change

15 between Study 1 and Study 2, you will see the results

16 are similar.

17   Now, it's important in all this debate to

18 realize that non-inferiority trials are not only

19 difficult to design, they're difficult to do. And

20 they're difficult to interpret. I want to tell you

21 there are very important operational characteristics

22 of a non-inferiority trial. If you do it sloppily,

1   you tend to bias it towards your hypothesis, a point

2   that Bob has made repeatedly. So this is a harder

3   trial to do than HOPE.

4   So we took a great deal of pains. First, we

5   tried hard to design the study so that it mirrors the

6   earlier robust trial of a proven comparator. I think

7   regulators are in the habit of approving a specific

8   drug at a specific dose, not a class as a whole.

9   Well, that's where we'll all do after today's meeting,

10 but whatever it is.

11   So that was as close as possible, and we

12 achieved it. So we used ramipril at the dose that was

13 used in HOPE, and we wanted an adherence that was at

14 least as good as HOPE and we achieved it. It was the

15 study with the clearest result.

16   The next thing was we minimized protocol

17 deviations, crossovers and drop-outs, and this was

18 incredibly low. The third thing was bias and outcome

19 acetate was avoided using proper definition, careful

20 documentation and blinded adjudication, and the trial

21 as a whole was blind.

22   The standard of care was at least consistent

1   with the standards of the prior trial, but indeed, it

2   was also consistent with modern standards so you can

3   apply it today. And an important word was clinically

4   relevant non-inferiority margin. ICH guidelines had

5   stated, and so have many commentators, that you come

6   to a non-inferiority margin not just on a statistical

7   exercise. It's a combination of clinical judgment,

8   what is clinically irrelevant, statistical expertise,

9   and the two together. And that's what I hope we can

10 do, and the key thing is did we have a margin that

11 will preserve a very high proportion of benefits

12 versus the comparator, and we'll look at that later.

13   Are the results consistent across subgroups?

14 The answer is yes, generally, they are. The hazard

15 ratio changes slightly. The confidence interval goes

16 up or down, but essentially, they're around the

17 central tendency of the comparator. And there were

18 other key quality indicators, patient characteristics.

19 Compliance was, in fact, better on ramipril in

20 ONTARGET than in HOPE. I'll show you that. And the

21 proportion of people who used the full dose was

22 greater in ONTARGET than on HOPE. And the

 1 completeness of follow-up was high and as I said, high

 2 study power.

 3   Here is the comparison. Let's first just

 4 look at these two columns. You will see percent of

 5 ACE inhibitor at the end of the study, 81 percent

 6 versus 79 percent, at least as good as HOPE but

 7 perhaps better. And if you look at those on a full

 8 dose, 83 percent versus 75 percent. And if you look

 9 at percent discontinuing drugs, fewer here than here.

10 Percent followed till the end -- this should be

11 removed here, four deaths -- but it's really very high

12 in both trials. And the same thing for the

13 telmisartan part, high proportion on the drugs at the

14 end, high proportion on the full dose, and high

15 follow-up. So the trial was done as well as could be

16 done.

17   Now, I've always believed that when you do

18 non-inferiority trials, you hope to see something that

19 benefits patients. And yes, as expected, we found

20 better tolerability with telmisartan compared to

21 ramipril. And this is the rate of discontinuation

22 over time. And you will see that although telmisartan

1   lowered blood pressure slightly more than ramipril,

2   there's a small absolute excess in hypertension.

3   That's not surprising, but serious hypertension like

4   syncope was similar.

5   But as expected, there's an 80 percent lower

6   rate of cough with telmisartan compared to ramipril,

7   not a surprise but nice to see that in this study.

8   And angioedema, which is a serious but rare

9   consequence of the use of ACE inhibitors, was also

10 significantly reduced. Half of these were not life-

11 threatening; half of these were life-threatening in

12 both groups. Renal impairment the same, and

13 obviously, this is the same thing that I showed you.

14 There was less permanent discontinuation of 10

15 percent.

16   Now, what can we conclude thus far? That

17 telmisartan is non-inferior to ramipril. The primary

18 composite outcome, that's the one-sided p-value. The

19 whole primary composite outcome, that's the p-value

20 against the 1.13 protocol specified margin. If you

21 use the FDA margin, it's 0.03 here for the primary

22 composite, an 0.01 for the key secondary outcome.

 1   Most of the benefits of ramipril are

 2   preserved, and I'll discuss that. I'll show you 95

 3   percent of the benefits of ramipril can be preserved,

 4   and on a worst-case estimate, about three-quarters.

 5   Consistent results are there on secondary outcomes and

 6   subgroups, and it's better tolerated overall.

 7   Now, let's move to the placebo comparisons.

 8   The first thing to say is TRANSCEND population is not

 9   the same as HOPE nor is it the same as ONTARGET.

10   There are subtle differences, and there's an obvious

11   difference. This group could not tolerate an ACE.

12   This is a different study. PRoFESS looked

13   at the effects of early initiation of telmisartan, and

14   the original design just said we want so many events,

15   no pre-specified length of follow-up. And 50 percent

16   of the events occurred in the first six months, so

17   it's incumbent on us to look at the data differently

18   from the first six months and later. And that was

19   also obvious from the sort of survival curves you'll

20   see didn't meet the proportional hazard assumptions.

21   So you could look at PRoFESS as a whole,

22   what telmisartan does on top of ACE and without ACE.

1 So this is almost like the ONTARGET. This has some

2 parallels to TRANSCEND. And this is an ACE

3 intolerant. I'm going to focus on TRANSCEND mostly and

4 briefly come to PRoFESS. Six thousand people in this,

5 504 events, 465, 40 fewer events and that is a hazard

6 ratio, .92, confidence interval of .81, 1.05, p-value

7 .22. Clearly, not significant, no question of that.

8   But the point we have to do is we've got to

9 ask ourselves, we've got a confidence interval here.

10 Where in that confidence interval is the real result?

11 Is it .92 itself? Is it at the better end of it or is

12 it really neutral, zero? And most of us here are

13 sensible. We think of evidence as a continuum and the

14 rest of our -- Bob, are you questioning that we are

15 sensible?

16   DR. TEMPLE: No, I think we were just

17 appreciating the praise.

18   [Laughter.]

19   DR. YUSUF: Thank you. I saw your eyebrows

20 go up.

21   Anyway, so what I am now going to discuss is

22 where here is the real effects by looking at a number

1 of things. Now, we did pre-specify a key secondary

2 endpoint, which is the whole primary endpoint. Here

3 we have 384 versus 440, a difference of 56. Remember,

4 the difference is 40 there on a fewer number of

5 events. And here's a 13 percent risk reduction with a

6 hazard ratio of .76 to 1, nominally significant p-

7 value, borderline result. Again, ask yourself is the

8 result 13 percent? Is it closer to, say, 20 percent

9 or is it really null? So where is the result in

10 reality?

11   The other thing is time. In the 4-fold

12 endpoint for about two or three years, there was no

13 difference, and then it started to convert. But the

14 3-fold endpoint, after about a year, you can see it

15 steadily keeps on widening.

16   Now, one point that Richard Peters always

17 told me is that our prevention trials are horribly

18 short. A five-year trial really is a

19 two-and-a-half-year trial. Why? Because events

20 happen from day 1 to the end of the trial and the

21 median time of two events is the midpoint. So a five-

22 year trial is really a two-and-a-half-year trial.   A

1   ten-year trial is really a five-year trial. What we

2   really need are 20-year trials. That's hard to do for

3   a variety of reasons.

4   So in a sense when this drug, or drugs like

5   this or a statin is used, people are not using it only

6   for five years; they're using it for life. So you

7   really want to consider not only what the trial showed

8   at the end but what it might show later. And this

9   requires judgment and statistical analysis. The

10 health economic field has formalized this. The rest

11 of the clinical trials field hasn't.

12   Now, let us now look at something else.

13 Patients are interested not just in preventing first

14 events. They're interested in preventing not only the

15 heart attack but should they be at risk of stroke

16 later, to prevent the stroke, and should they be of

17 death later, to prevent the death. They're interested

18 in the total burden of disease. And here when you

19 look at that, these are the data on the first events

20 from the 4-fold endpoint, 465 versus 504 and 40

21 difference. But when you look at total events, you're

22 getting 640 versus 745, a 105 difference. So the

1   numbers of events have only gone up by about

2   200 -- you have 50 percent -- but the difference has

3   doubled from 40 to 105, more than doubled. And you'll

4   see that right across everything except death, there

5   is a even more marked difference.

6   This slide helped me in two ways. It helped

7   me think through a dilemma I always had after this

8   program. Why did we not see an effect on heart

9   failure? It bothered me a great deal. But I think we

10 just had a bad break, play of chance, because when you

11 look at multiple events, it starts to tend to go the

12 way you expect it would go.

13   The other way it helped me was at the .92

14 hazard ratio, is that real? Where in the confidence

15 interval is the truth? Well, this is telling me the

16 truth may be closer to .87. Now, this is nominally

17 significant using what is called a sandwich variance

18 estimator.

19   I'm not a statistician. But I'm told that

20 this method controls for the correlation between

21 multiple events in the same patient and there are two

22 other methods that I know of. One is the Cook and

1   Lawless method that essentially gives a somewhat more

2   extreme p-value, and the Poisson regression method

3   that gives a much more extreme p-value. But they're

4   all assumption models. So we chose the most

5   conservative of these to just show you that there is

6   an effect.

7   The key thing is not the p-value. The key

8   thing is that when you look at the totality of the

9   burden of disease, it starts to reinforce there's a

10 treatment effect. And this is permanent

11 discontinuation. This is giving you a global look at

12 tolerability. And what you see is telmisartan is, if

13 anything, better tolerated than placebo. This seemed

14 to me, miracle but so I don't really believe it's

15 better than placebo, but I believe it's no worse than

16 placebo. And that's good enough for me.

17   Now, the other thing is in understanding a

18 trial, you need to look at many aspects. What

19 happened to concomitant therapies? Were there

20 treatments that counteracted potential benefit of your

21 drug? And so we looked at random treatments post-

22 randomization, things that saved lives. Anti-

1   platelets started off at about 80 percent, remained at

2   about 75 percent in the two groups, no differential.

3   But beta blocker use was slightly higher in the

4   placebo compared to the telmisartan group. Diuretics,

5   much higher than in HOPE, HOPE was 15 percent. This

6   is twice as often, and moreover, there is a

7   differential. Why? Well, you can't use an ACE

8   inhibitor. You can't use an ARB because this is a

9   trial of ARB, so people reach out for diuretics or

10   calcium blockers. And there is a marked difference,

11   and this difference is in favor of the placebo group.

12   And that tends to make it harder for any drug,

13   telmisartan or anything else, to show a result.

14   There are two ways to interpret it. You can

15   say what I really want to know is what telmisartan

16   does on a strategy basis, and it's all there. But

17   another way to interpret is could this have an effect

18   on the treatment itself. And yes, of course, it

19   would. We know diuretics and calcium blockers and

20   beta blockers are good drugs and that will tend to

21   narrow down the differences, biasing the results

22   against telmisartan.

 1   So now let's look at the combined analysis

 2   of PRoFESS and TRANSCEND. And I want to make some

 3   points, which may have been misrepresented in the

 4   briefing document. First, I want to say this was pre-

 5   specified by the academic leadership of both PRoFESS

 6   and TRANSCEND. I was the chair of this study. I was

 7   the co-chair of this study with Chris Diener and Ralph

 8   Sacco. And we wrote a document well before TRANSCEND

 9   and PRoFESS was unblinded, and it's dated 2007. And

10   on my prompting, the sponsor was able to find it.

11   Second point I want to say, in PRoFESS, we

12   observed a timed to treatment interaction and,

13   therefore, in TRANSCEND, we also looked at exactly the

14   same time cutoff. And it's there in our paper, in The

15   Lancet, and I'll share that with you.

16   The sponsor did not pre-specify these

17   analyses in its statistical plans. But I'd like to

18   tell you that I as a academic person did pre-specify

19   this and pre-specified this in between based upon what

20   I saw in PRoFESS when I examined TRANSCEND. So it's

21   not post-talk as was stated in the sponsor's

22   statement, and it obviously misled the FDA reviewers.

1   Now, these are data on the meta-analysis on

2   all patients, including people who are receiving ACE

3   inhibitors in TRANSCEND and PRoFESS, 26,000 people and

4   you will see 15 percent down to 14 percent, 7 percent

5   risk reduction and nominally significant confidence

6   intervals here.

7   I want to point out that two-thirds of the

8   events here come from PRoFESS, of which half come in

9   the first six months. So a third of events comes at a

10   time where you expect treatment not to have an effect.

11   So we really need to look at this separately under six

12   months and beyond six months, and we'll do it later.

13   If you look at CV death, MI and stroke,

14   similar results, slightly better hazard ratio,

15   slightly tighter confidence limit, slightly better p-

16   values. But these are saying, well, there is some

17   effect, some moderate effect. And you've got to

18   debate whether this is clinically worthwhile or not.

19   The second thing is looking at people not

20   receiving ACE inhibitors because based on the combined

21   arm of ONTARGET, we're not going to use dual therapy.

22   And when you do that, the results are consistent, both

1   for the quadruple endpoint and for the triple

2   endpoint, and the hazard ratio's a little better. The

3   confidence limits are about the same, and the p-values

4   are a little better than what I showed you on the

5   previous slide.

6   So the totality of evidence from the

7   placebo-controlled trials is not saying there is no

8   effect. It says there is an effect. There is a

9   moderate effect. And you've got to decide whether

10   that effect is worthwhile for patients and whether

11   clinicians can use it.

12   This is the time effect. The 4-fold

13   endpoint, about one and a half years it diverges.

14   Actually, when you look at the thing, it was at six

15   months. And here at 3-fold, you will see somewhere

16   about eight, nine months, you'll see the divergence.

17   But when you look at it month-by-month, at six months

18   is the breakpoint. And you will once that's been

19   finished, it keeps on diverging, which means it's an

20   interpretation. It's an extrapolation. Longer-term

21   follow-up might -- and the word is "might" with an

22   underline -- might produce this diverging effect at

1   greater clinical benefit.

2   We did show this with the 12-year follow-up

3   of the SOLVD prevention trial. I don't know if many

4   of you saw it. When we finished SOLVD at three years,

5   there was an 8 percent reduction in mortality that was

6   not significant. But we then did a 12-year follow-up

7   doing death registries, and then we had a much larger

8   and a highly significant reduction in mortality with

9   12 years of follow-up. So this again speaks to my

10   point. Our trials are simply too short.

11   So this is the data split by under six

12   months and over six months. The quadruple endpoint,

13   if anything a slightly adverse effect early, but

14   whether that's real or whether it's the player chance,

15   I don't know. Certainly, no benefit. And after six

16   months, now it's a 13 percent risk reduction. My

17   statistician friends will immediately jump up and say

18   you can't put a p-value there; this is a conditional

19   analysis.

20   What I really want you to see is that

21   benefits really accrue after six months. And then

22   when you do that, the effects are around the 13 to 15

 1   percent range. That's the point I want to get across

 2   to you.

 3   Now, there are various ways that you can

 4   calculate or estimate what the benefits of telmisartan

 5   in ONTARGET would have been had we been able to have

 6   an arm with a placebo. And this is an imputed

 7   calculation. It has some assumptions. The most

 8   important assumption is that the conditions under

 9   which you do the trial have not materially altered the

10   sensitivity of the trial; that is, assay sensitivity;

11   that ramipril today, despite the changes in patient

12   risk and despite concomitant therapy, will still be

13   approximately as effective. And hence, you can derive

14   it.

15   Essentially, you take the HOPE result, you

16   take the ONTARGET result, you do some mathematical

17   calculations. It's really -- to a simplistic person

18   like me, it's a multiplication, but it's a little more

19   complicated than that. But conceptually, it's a

20   multiplication of these two. You get a hazard ratio

21   of .79. You can derive your confidence interval. And

22   when you do that, something interesting emerges, which

1   is based on ONTARGET, you would say that half the

2   conditions between ONTARGET versus HOPE, not change,

3   in terms of assay sensitivity, you'd prevent 95

4   percent of the benefits of ramipril. And if you were

5   a pessimistic sort of chap and used the worst

6   confidence interval, you'd say, well, I can guarantee

7   at least   two-thirds of the benefits would be

8   preserved.

9   This is important because ultimately, that's

10   what non-inferiority trials are aiming at. I don't

11   want to lose most of the benefit of my active

12   comparator. It's not a p-value. It's not a margin.

13   This is the calculation that is relevant.

14   The next thing is if you look at the

15   totality of the evidence on different ways of looking.

16   So this is the imputed placebo, which I've shown you

17   -- sorry. This is HOPE. This is the imputed placebo

18   in ONTARGET telmisartan versus ramipril.   Therefore,

19   telmisartan versus placebo. This is TRANSCEND on the

20   triple endpoint. That's the thing, just touches the

21   axis nominally significant. This is PRoFESS and

22   TRANSCEND together. Point estimate is worse than

1   this, but the confidence interval is better. This is

2   a subset of this. Similar results, this is beyond six

3   months, a result that is closer to the TRANSCEND 13

4   percent risk reduction.

5   What this is telling you is no matter which

6   way you look at the result, there is some benefit

7   there, which I think is clinically beneficial. It's

8   somewhere in the 13 to 15 percent range in the active

9   placebo trials. Even if you buy that times have

10 changed since we did the HOPE results and even if you

11 say I don't buy your argument, Dr. Yusuf, this

12 population is the same as ONTARGET, which I'm pointing

13 out to you, I'm not sure that the TRANSCEND and

14 PRoFESS population is the same as ONTARGET. So there

15 is evidence of efficacy in the modern era.

16   So thus far, the summary of the data in

17 people with vascular disease is in ACE-tolerant

18 individuals. Telmisartan is non-inferior. And

19 therefore, it means from a clinical sense, it is

20 similar within certain bounds and as I said, two-

21 thirds of the benefits prevented. This will be the

22 point estimate, but really use the whole confidence

1   interval. And obviously, if you were formalistic, in

2   ACE-intolerant people, you don't have a significant

3   reduction versus on the 4-fold endpoint, but it tends

4   to be superior. It's not a slam-dunk result by any

5   means. And this is supported by the fact that there

6   is a nominally significant reduction of 13 percent

7   with confidence intervals that are fairly wide.

8   Now, the meta-analysis done in many

9   different ways suggests there's a benefit of somewhere

10 from to 7 to 14 percent and the results are around

11 that.

12   Now, to the second half of my presentation,

13 which I must say I enjoyed more preparing than the

14 first part. This one was prepared after I saw the

15 last set of questions that the FDA posed. And I'd

16 like to take 10 to 15 minutes to sort of share my

17 perspectives on it. The questions that I want to deal

18 with, which are the questions the FDA has raised for

19 the panel and in a sense was paraphrased by Dr.

20 Stockbridge, what is the right non-inferiority margin?

21 What is the right choice of reference for a non-

22 inferiority study? Constancy. What is the role of

 1 constancy? Fixed versus random effects model if you

 2 went down the path of a meta-analysis.

 3   I'd like to remind everybody in this room,

 4 and I'm sure you share this, is that the approach in

 5 non-inferiority trials should integrate clinical and

 6 statistical judgment. This had been stated by many

 7 people who write about non-inferiority trials. It's

 8 not just a statistical exercise. It's both. And it

 9 needs to -- and this is my addition. It needs to

10 consider the totality of the evidence, not one p-

11 value, not one endpoint.

12   So even if that pre-specified single

13 endpoint just about meets your criteria, if the rest

14 of the trial looks bust, then believe the rest of the

15 trial; or reverse, if the pre-specified endpoint is

16 borderline, look at the rest of the data to tell you

17 is that a real measure. And therefore, to look at the

18 measure of total burden of disease because that's what

19 patients care about and that's what clinicians care

20 about.

21   Actually, in another curious sense, that's

22 important because one thing that non-inferiority

 1   trials has done is pushed us to have trials about two

 2   to four times larger than superiority trials. Now, if

 3   we start to push the margins down, which is one of the

 4   things people are trying to do, you just can't have

 5   trials eight to 10 times larger than good trials.

 6   Well, then we need to think of a way where we get more

 7   relevant endpoints. So actually, that last point has

 8   a statistical value in the thinking as well.

 9   So which non-inferiority margin to use is

10   the question to you, gentlemen? 1.13 proposed by the

11   sponsor, 1.085 proposed by the FDA. And yesterday,

12   when I saw the most recent questions, we learned that

13   the FDA would like discussion of the 99 percent

14   confidence interval to be used when the reference

15   trial is a single trial. That is a really interesting

16   academic exercise. I'd love to get into it, and maybe

17   in the meeting on non-inferiority trials we're going

18   to discuss in September, we can into this. I mean

19   what is the implication? This to this is a doubling

20   in size; this to this is another doubling in size.

21   It's very simple. So from this to this is a full fold

22   increase in size. So HOPE was 10,000. This is

1   25,000. That would be 55,000, and this will be about

2   70, 80,000. So I'm all for it. It keeps me in

3   business.

4   Now, let us stop aside. The question is not

5   so much about the non-inferiority margin once a trial

6   is finished. After the trial is completed, what

7   really matters is what are the results? What percent

8   of the benefits are preserved? Are there data inside

9   the trial that informs us as to whether what we are

10   claiming is supportable? Are there data outside the

11   trial from similar trials that could support the

12   findings? And that's the way I'd like to go about it.

13   First, if you take -- based on ONTARGET,

14   telmisartan versus ramipril, if you take the triple

15   endpoint, it's about 100 percent. You preserve all

16   the benefits. And if you used a cautious approach,

17   you'll preserve three-quarters of the benefit. And if

18   you take the quadruple endpoint, it's 95 percent. But

19   these are the same numbers, and on a cautious

20   estimate, you will preserve two-thirds of the

21   benefits. This meets both the protocol specified non-

22   inferiority margin as well as the FDA margin, and this

1 does not meet the FDA margin but meets the protocol

2 margin.

3   The key thing is not so much the margins.

4 The key things are these: Is preserving 90 to 100

5 percent or 66 to 74 percent on a worst-case analysis,

6 are these clinically useful? That's the question.

7 The next question is can I have some confidence in

8 what I saw here in ONTARGET. And let's look at the

9 total number of events.

10   First, when you look at total numbers of

11 events, telmisartan versus ramipril, individual

12 events, 1400 versus 1400. When you look at all

13 events, it's 2,000 versus 2,000. so 4,000 events, and

14 there's not a shred of a hint of a difference here.

15   So here, this is the hazard ratio and this

16 is the sort of confidence interval using the sandwich

17 variance estimation.

18   Let us look at TRANSCEND total number of

19 events. Again, 465 versus 504, this is the quadruple

20 endpoint. That's the difference, a difference of

21 about 40-something. And there is here, total number

22 of events, 640 versus 745, 105. Again, gives us

1 confidence that the results in TRANSCEND are real.

2 And this is again the data.

3   What about cardiovascular hospitalizations?

4 This is first hospitalizations. And in ONTARGET,

5 remember, it's non-inferiority. So we're seeing

6 telmisartan versus ramipril, 5,000 events equally

7 spread. Look at total hospitalizations, 10,700 events

8 equally split. There's really not even a hair's

9 breath between these two numbers in the wrong way.

10   TRANSCEND, total number of hospitalization,

11 750 versus 821 for first, all hospitalization, 1600

12 versus 1849. And these are the hazard ratios. So

13 you'll see looking at the totality of the evidence on

14 hospitalizations, it again reinforces similarity

15 between ramipril and telmisartan, and looking at that

16 of telmisartan versus placebo, it reinforces

17 superiority so that these two are really quite

18 persuasive for me.

19   The other thing is let's look at data

20 outside the trial, and these are the data on ONTARGET,

21 the triple endpoint telmisartan versus ramipril,

22 that's the result. This is the Valiant endpoint. On

1   Valiant's primary endpoint, you will see similar

2   results. These are risk ratios. That's why the

3   confidence limits are a little tighter than the hazard

4   ratios. So we have strong external support. We have

5   strong support within the trial when you examine the

6   data every which way.

7   Now, what choice of reference study? First,

8   let me tell you, if you use HOPE, you get this. If

9   you use HOPE plus EUROPA, you get this. And if you

10   use HOPE, EUROPA and PEACE, you get that. If you take

11   all the heart failure studies, you get that. If you

12   take all the trials in the literature, you get that.

13   Now, look at the confidence limiters. Are

14   they really the same confidence interval? Are we

15   going to dance on the head of a pin saying 8.87 is

16   different from .88 or .9? So the totality of the

17   evidence, when you look at the extreme end of the

18   confidence limits, are they really very, very similar?

19   What it's also telling you is something very

20   curious. What it's telling you is over a 20-year

21   period when these trials were done, the effect sizes

22   in some were different, not identical populations, is

 1 about the same. So over a 20-year period, despite the

 2 fact that these people have five times to 10 times the

 3 event rates of these people, there's constancy in its

 4 effects.

 5   Now, we are fortunate in the ACE inhibitor

 6 field because there is superb data with which you can

 7 look at it. Now, really I don't think when you have a

 8 good reference trial, you do a meta-analysis. You do

 9 a meta-analysis when your individual trials aren't

10 good enough. And the reason for it is not every trial

11 is done well. Not every trial is done with the right

12 drug at the right dose. And in the end, FDA and all

13 regulatory agents and clinicians will use one drug at

14 one dose or a dose that you've proven to be effective.

15 So we're not asking the question what does telmisartan

16 do against the whole world of ACE inhibitors. We're

17 asking the question what does telmisartan do against

18 the best available evidence that comes from a good

19 trial or off a good ACE inhibitor in a specific

20 population at a specific dose.

21   The FDA, one of the questions that asked is

22 are the benefits from HOPE overestimated because it

1   was stopped early for efficacy. I must say this is a

2   difficult one for me to deal with. But I want to tell

3   you how we monitored the trial, and then you get a

4   judgment whether or not, and if you do, to what extent

5   you need to dampen down the HOPE results. We used a

6   slightly different method of monitoring compared to

7   the standard O'Brien-Fleming method, which is where

8   this business of overestimation came.

9   The red line, and if you extend it all the

10   way, is called the Peto-Haybittle method, which is

11   three standard deviations throughout. We used in all

12   our trials a modified approach. That is in the first

13   half, you need to cross four standard deviations. In

14   the second half, you need to cross two standard

15   deviations, but that is not enough. You need to cross

16   it twice at any given time consecutively and it needs

17   to remain crossed for six months. So it's not one

18   blip. It's an extreme boundary, and it's got to cross

19   it and remain crossed. And these are the results.

20   As early as '96, the study was nominally

21   significant. One year later, still significant.

22   Again, a year later, highly significant. Then they

1   decided, let's invoke the rule of the second look. So

2   they looked at it a second time. Yes, still highly

3   significant. Same effect size but more data, so that

4   value gets bigger. And this is the end of the trial

5   when we did the sweep of the data and got the data.

6   So three times we remained beyond an extreme boundary.

7   Now, I know my statistician told me how she

8   can adjust for the p-value, which means it's the sixth

9   or seventh decimal point. I don't know how they

10 adjust the effect size, and there may be cleverer

11 statisticians who would be here. But I think my sense

12 is you only adjust it for a tiny amount, if you have

13 to adjust it. So this is not a temporary blip.

14   The next issue, which is the toughest issue

15 in non-inferiority trials, is the concept of

16 constancy. And in the last week, I spent a lot of time

17 thinking about it because I found, to me, I was

18 surprised there was a debate on this issue. There is

19 many people I respected like Janet Wittes said, "You

20 know, Salim, this is the thing that bothers me the

21 most about the field." And I think the response to

22 constancy has been let's tighten the confidence

1   interval so that I don't want to take a risk. Let's

2   take smaller and smaller risks. Well, that is one

3   approach, but there are other approaches.

4   The other thing is people misunderstand

5   between constancy and effect, which is the relative

6   risk, versus constancy and absolute event rate,

7   which -- let me give you an illustration. If I did

8   the HOPE trial, I can find low-risk people with a 2

9   percent event rate and high-risk people with a 5

10 percent event rate per year. So the fact that my next

11 trial has 3 percent and my previous trial had 5

12 percent is irrelevant because you can always get

13 groups with different inherent risk. What needs to be

14 constant is the sensitivity. So the relative risk did

15 not differ importantly over different circumstances.

16   I think it is impossible, at least from what

17 I know, to examine prospectively the data. But in a

18 rich field like the ACE inhibitor trials or the statin

19 trials, you can turn your telescope backwards and look

20 at 20 years of excellent data, and that's what I've

21 done. Therefore, what I've done is I've looked at

22 whether the relative risk reductions have changed over

1   a 20-year period in different risk groups and by

2   marked changes in concomitant therapy.

3   The concept of discounting comes from a

4   concern of diminishing relative benefit. It hasn't

5   been proven, at least in cardiovascular, but that's a

6   concern. It's a legitimate concern, but how

7   legitimate, and that's what I'd like to talk about.

8   So here are the large trials, eight trials,

9   publication '91 to 2004. Obviously, this study,

10 which, obviously, I was the project officer of, was

11 designed in 1984. So really, this is a 20-year period

12 over which these trials were done. We have 22,000

13 people. We have five and a half thousand events. No

14 field is so rich.

15   So if you look at the relative risk and you

16 look at that .86, .88, .86, .81, .86, .78, .83, .83,

17 they're all hovering around a central tendency. And

18 if you did a formal test of heterogeneity across this,

19 there really is no evidence of heterogeneity across

20 these trials. You shouldn't go by p-values. You

21 should by the relative risk and the confidence

22 intervals.

1   So there's really no evidence that the

2   benefits of ACE have changed over 20 years. So you

3   could ask yourself is it therefore reasonable to

4   postulate that it has changed in 10 years, and it's

5   the last 10 years of these trials.

6   The next thing therefore is let us look at

7   within a trial by risk. So this is the p study. I

8   wasn't able to get the data from the p study by risk

9   groups, but I got it in HOPE and I got it in EUROPA.

10   I want to take you through this. So in

11 HOPE, the low-risk people had 2 percent per year, the

12 median risk, 3.6 percent per year and HOPE had 6

13 percent, and the high risk had 6 percent. Look at the

14 similarity and consistency of risk over this period.

15 The same thing in EUROPA, one and a half percent low-

16 risk, two and half percent, 4 percent, similarity, no

17 obvious statistical heterogeneity.

18   Take the LV dysfunction heart failure

19 trials. Some of them have a 22 percent one-year event

20 rate. That's the AIRE study. Others have a lower

21 event rate. Again, similar results.

22   So what's this telling you from as low as a

1   one and a half percent annual event rate to as high as

2   a 22 percent annual event rate? There is no apparent

3   evidence of heterogeneity of treatment effects. So

4   this will tell me across different risk groups, I

5   should not worry too much about constancy.

6   What about other treatments? So this is

7   EUROPA and HOPE put together, and you will see lipid-

8   lowering agents, that's a benefit. As a background,

9   no lipid-lowering agents, similar results. And note,

10   this is what changed markedly between HOPE and

11   ONTARGET. Beta-blockers, no beta-blockers, no obvious

12   heterogeneity.

13   This is all the drugs. This includes

14   anti-platelets as well. So anti-platelets,

15   lipid-lowering and beta-blockers all together, that's

16   the effect. This is none of the above. That's the

17   effect. And this is one of the above and two of the

18   above. No real evidence of heterogeneity. That's

19   what the interaction p-value is.

20   Well, throw in re-vascularization into the

21   mix. No re-vascularization, no obvious heterogeneity.

22   Now let's do something. Let's take re-vascularization

1   plus anti-platelets plus lipid-lowering plus beta-

2   blockers. Again, that's the treatment effect, and

3   this is with re-vascularization but none of the drugs.

4   What this is telling you is that two

5   relevant things that we know as a clinician that has

6   changed over time, there is no evidence of a lack of

7   constancy. You can never prove constancy. So this

8   then has to ask yourself is there even a need to

9   discount. If there is a need to discount, do you

10 discount moderately? Do you discount hugely or

11 incredibly hugely? That's an academic question.

12   Now, here is what I've shown you again, that

13 the benefits, the results of telmisartan versus

14 ramipril are similar across risk groups and similar

15 whether or not you use statins.

16   Now, so my summary of the exploration of

17 constancy in this field is that we've got consistency

18 of clinical benefits over 20 years. Fifteen years is

19 the range of publication dates. Twenty years is from

20 start of design to finish. Over a 10-fold range of

21 patient risk, over a range of concomitant therapy, and

22 we are luckily in a field where we can test our

1 assumptions. We don't need to just theorize. We can

2 test it.

3   Now, this is something I love, and I can

4 spend an hour on it, but I won't. First, I want to

5 say this is the effect issue of random effects versus

6 fixed effects. As you know, I've been with the meta-

7 analysis field and written on it and published many

8 for the last 25 years. And I do want to address this

9 briefly, but I want to say, to me, this is not a

10 relevant issue for today. I think when you have a

11 high quality, robust trial such as HOPE, that's what

12 you use because we want to compare against a specific

13 drug at a specific dose at a specific population. And

14 my friends told me don't even discuss this, but I

15 can't help but discuss this. So since you asked, I'm

16 going to tell you what I think.

17   First, I think the word "fixed effects

18 model" is a misnomer. A better term is an

19 "assumption-free model" or a "simple weighted

20 average." It's a simple method. Even I can do it on

21 a calculator. And most of you, I can teach you how to

22 do it on a hand calculator. It's reproducible. If I

1   do it and you do it, we're going to get the same

2   results because it's assumption free. It's model

3   independent.

4   It's simply a weighted average. Large

5   trials are more informative, so you weight them more.

6   Small trials are less informative, so you weight them

7   less. If you decide you wanted an indicator of

8   compliance like in the cholesterol-lowering trial,

9   large amount of lipid-lowering, small amount of lipid-

10 lowering, you can add it as a covariate. That's an

11 informative way of doing it. And it describes what

12 the trials have shown. I've got these trials. This is

13 my result. It's not pretending to tell you what the

14 future might be. It's just telling you this is what

15 I've got. And it's been found to be reproducible.

16 When you do a meta-analysis of large trials and you

17 further then do a   meta-analysis, you're able

18 to predict the results of the trials.

19   The random effects model assumes something.

20 It assumes that the trials you've included are

21 randomly identified from the universe of trials. Who

22 ever believes that? We actually know that's not true.

1   Second, there is a term for between study variance,

2   and all it's doing, it's assuming that, statistically,

3   you can adjust for the variation between trials. But

4   we know the variations between trials relates to the

5   patient populations, to co-therapy, to the way the

6   study was conducted, compliance, the dose used. And

7   two drugs in the same class are not necessarily

8   identical even if each of them was shown to be

9   beneficial.

10   So to assume that the entire variation

11   between studies is simply a statistical fact is

12   missing the picture. And we assume that the results

13   apply to a random set of patients, which we know is

14   entirely untrue. And I want to give you an example

15   that by and large, most of the time you get similar

16   results, the random effects model gives you slightly

17   bigger confidence interval in general, but sometimes

18   it can give you nonsensical results. And the reason

19   for that is random effects model weights small trials

20   disproportionately greater than they do large trials,

21   especially when there's variation. And I've found

22   several examples in the literature, and I'm going to

1   just show you one example of magnesium in acute MI.

2   Now, I was interested in this field, and

3   about 15 years or 20 years back, Dr. Teo, first

4   author, Richard Peto, Rory Collins and I was the last

5   author, we published a meta-analysis in the BMJ that

6   claimed that magnesium was magic, 50 percent reduction

7   in mortality, that's the relative risk reduction,

8   cheap, safe drug. And in fact, I wrote an editorial

9   in circulation, probably the editorial that I have egg

10 on my face on, a miracle drug for the whole world or

11 something like that. It just shows you even I can be

12 wrong.

13   So a limit to a moderate-size study that tended

14 to support it but wasn't convincing. I was part of

15 the steering committee that designed the large ISIS-4

16 study based on these data. We had 60,000 people, and

17 when the results were finished, it was absolutely no

18 benefit, if anything, harm. Dr. Antman from Harvard

19 did not believe this. He said this was done by those

20 stupid Brits. We Americans can do a better trial, and

21 so he did a big trial, 6,000 patients, same result.

22   Now, what happens with a simple weighted

1 average, assumption-free method? Well, the 66,000

2 will outweigh this, and now we have 70,000 people,

3 hazard ratio, a risk ratio of 1, a tight confidence

4 limit, wholly non-significant. Who on earth believes

5 magnesium works? But use a random effects model and

6 what do you get? You get benefit, .67 and curiously,

7 a confidence limit where the upper confidence limit is

8 well away from 1.

9   So this is a very good example of how

10 inherently flawed the random effects model can be.

11 And I can at least give you one or two other examples

12 on hard endpoints where this has happened.

13   So I want to now summarize. I want to

14 summarize that the ONTARGET study has clearly shown

15 that telmisartan is non-inferior to ramipril. This is

16 using the protocols specified, sort of non-inferiority

17 margin. This is using the FDA margin. This is on the

18 border. This endpoint is clearly below it. And if we

19 wanted to put p-values, that's 0.03. And remember,

20 the reference should be 0.025. And here the reference

21 is 0.025, but this is 0.01. So it's there.

22   Different ways of looking at additional data

1   all suggest different effect sizes ranging in about 10

2   to 20 percent range, probably with a central tendency

3   around 14 percent. But it all suggests benefit. It's

4   not you meet a p-value, you succeed or fail. I'm

5   looking at evidence on a continuum.

6   When you look at the total burden of

7   disease, which is total number of events, it

8   reinforces that there's a treatment effect in the

9   placebo-control trials and reinforces similarity

10 between ramipril and telmisartan based on 10,000

11 events. That's what total number of cardiovascular

12 hospitalizations are. So everything, the totality of

13 the evidence related to telmisartan shows that in a

14 high-risk population, we seem to preserve almost the

15 same benefits of ramipril but in a cautious view, we

16 preserve somewhere between two-thirds and three-

17 quarters.

18   There are supportive data for multiple

19 events and hospitalization analyses. And in the

20 placebo-control trials, of related but not the same

21 population, we saw telmisartan has a modest effect or

22 a 8 to 15 percent, some would say moderate. And it

1   increases with time. So you've got to take that in

2   your thinking. As a clinician, I would. And it

3   occurs on top of many other proven therapies.

4   Therefore, ladies and gentlemen, I would

5   like to conclude that the totality of the evidence

6   indicates that there's a clinically important benefit

7   of telmisartan in high-risk patients with vascular

8   disease. Thank you very much.

9   I meant to introduce Jeff Friedman. So Jeff

10 Friedman, and you can see his titles. He's pretty

11 grand.

12   DR. FRIEDMAN: Thank you, Salim.

13   I'm here today to give you a brief overview

14 of the safety of telmisartan. Given the focus of this

15 hearing and the questions put out by FDA, I'm going to

16 be brief. But on the other hand, in the briefing

17 document that we provided the committee members, there

18 is extensive information, and we are available to

19 discuss any and all aspects of the safety of

20 telmisartan here today.

21   Telmisartan has been well characterized in

22 the hypertensive patients due to its over ten years'

1   worth of marketing experience and substantial

2   exposure. And as pointed out, its profile is

3   consistent with those of other angiotensin receptor

4   blockers. The drug has also now been well

5   characterized in patients at high risk for

6   cardiovascular disease. As Professor Yusuf has

7   pointed out, the extent of information available

8   focusing on efficacy, but we have the same large body

9   of safety data.

10   With regard to adverse events, Professor

11 Yusuf presented the information that telmisartan is

12 better tolerated than ramipril and certainly

13 equivalent to placebo. And the adverse event and

14 serious adverse event profiles are consistent with

15 current labeling and the class.

16   For renal observations, drugs which impact

17 the renin-angiotensin-aldosterone system have a

18 certain adverse event profile. And we see the same

19 profile for telmisartan with no differences between

20 telmisartan and ramipril.

21   For sepsis, we observed low rates of sepsis.

22 However, there was more in telmisartan compared to

1 placebo with similar rates for telmisartan and

2 ramipril. Known factors predicting sepsis, such as

3 prior cancer and infection, were also shown to be

4 present in these trials. There was no clustering of

5 risk in any subgroups so that there's no group of

6 patients where a use of telmisartan appears to be

7 differentially adverse. And also, there's no

8 mechanistic explanation identified within our

9 pre-clinical data. No other ARB data suggests that

10 there is a sepsis issue present. However, we did add

11 such information to the label to be informative.

12   With regard to malignancies, there was a

13 higher rate of malignancies in the combination arm

14 than in ONTARGET. However, similar rates were

15 observed for telmisartan and ramipril as well as

16 telmisartan and placebo in the other trials. There

17 was no consistent pattern with regard to malignancy

18 data in the studies for the treatments and across

19 tumor types in particular. And there's been no

20 reported increase with malignancies with other ARBs.

21   With regard to our pre-clinical data, we

22 have two-year carcinogenicity studies in two species.

1 We saw no carcinogenic effect, and there is no

2 mutagenic effect observed with telmisartan. And we

3 have concluded in consultation with several experts

4 that telmisartan does not lead to an increased risk of

5 malignancy, which is consistent with what we believe

6 the FDA has put in their briefing document.

7   To summarize, the safety of telmisartan has

8 been well characterized in hypertensive patients and

9 now also in patients at high risk for having

10 cardiovascular disease. Telmisartan was shown to be

11 better tolerated than ramipril. And the trials that

12 were completed were sensitive enough to detect

13 differences between the groups with regard to safety,

14 which also would suggest to us that they have the

15 ability to detect the differences between efficacy in

16 the treatment groups should it have existed.

17   We would conclude that telmisartan is safe

18 for use in high-risk patients. And with that, I'd ask

19 Jim Young to come up and summarize for us.

20   DR. YOUNG: Well, thanks, Jeff.

21   Let's maybe lighten some of the discussion

22 up a little bit and bring it back into the clinical

1   arena, remembering again what Dr. Stockbridge pointed

2   out this morning about the importance of synthesizing

3   all of the available data. We do believe, and I

4   believe, that from the patients' and the clinicians'

5   perspective, telmisartan is an attractive option to

6   reduce morbid cardiovascular events in high-risk

7   individuals. And this is based on the fact that using

8   the a prior defined parameters in the clinical trials

9   discussed, as Dr. Yusuf has talked about in detail,

10   telmisartan was similar to ramipril, which was studied

11   in our HOPE trial.

12   All of these trials were done in patient

13   populations at risk for morbid CV events, and so a

14   very relevant target for therapy such as this. And

15   our observations should be put into the context of the

16   fact that clinicians often use an ARB, because of a

17   more attractive side effect profile, to achieve

18   various therapeutic endpoints. Particularly important

19   was the observation that telmisartan was better

20   tolerated than ramipril with more patients on target

21   dose at follow-up and few discontinuations due to side

22   effects.

1   Now, there's been reference to clinical

2 trials, and they are extraordinarily important,

3 particularly to provide high quality safety and

4 efficacy data that will guide our decision making,

5 particularly with respect to choice of strategies,

6 specific drug, and perhaps as important, specific drug

7 doses while managing our patients.

8   For example, Valiant and OPTIMAAL compared

9 two different ARBs, valsartan and losartan, as seen

10 from the life table curves here, to the ACE inhibitor

11 captopril in different populations but demonstrated

12 distinctly different observations with valsartan being

13 comparable to captopril in Valiant while losartan went

14 the other way and perhaps was more risky than

15 captopril in OPTIMAAL. This emphasizes the importance

16 of this clinical trial approach.

17   Now, data has been presented today and

18 represented by this figure indicating that reduction

19 to the tripartite HOPE endpoint of cardiovascular

20 death, MI and stroke with telmisartan was similar to

21 the observations in HOPE of ramipril versus placebo.

22 And furthermore, the primary composite ONTARGET

1   endpoint, which added hospitalization, which has been

2   addressed as well by Salim, met the a prior definition

3   of   non-inferiority.

4   I think this observation of non-inferiority

5   of telmisartan to ramipril really needs to be put into

6   the clinical context of adherence rates for ARBs when

7   compared to any hypertensive agents in a, quote, "real

8   world," unquote, setting. And I've chosen this data

9   from the Saskatchewan health database in honor of our

10 PI, Salim. And it demonstrates the substantially

11 higher adherence rates for ARBs than other drugs. It

12 should be remembered that in ONTARGET and TRANSCEND,

13 adherence rates were even higher as would be expected

14 in a clinical trial that was prescreened for patients

15 who could take the drug and then had a run in

16 treatment period.

17   So again, the safety profile of telmisartan

18 is robust with a total observation time in the three

19 outcomes trials discussed today about 180,000 patient

20 years. And there's been 10 years of experience with

21 this drug out on the market. And so again, as

22 mentioned, the adherence to the full 80 milligram

1   telmisartan dose at two years in ONTARGET was

2   substantially greater than ramipril, as you can see in

3   the bottom line on this slide. And when viewed

4   amongst the panoply of side effects that would cause

5   problems with using an ACE inhibitor, the RAAS

6   modulating agent side effects, there was significantly

7   less discontinuation of study drug for any reason.

8   So as you have seen, our conclusion based on

9   the totality of evidence and synthesizing all of the

10 elements related to clinical trial design,

11 non-inferiority issues, considerations of constancy

12 and whatnot, are that telmisartan is non-inferior to

13 ramipril with respect to the primary composite outcome

14 and the tripartite HOPE trial primary endpoint outcome

15 with most of the benefits expected with ramipril

16 preserved.

17   There was consistency of results on a range

18 of secondary outcomes and subgroups. And furthermore,

19 telmisartan appeared better tolerated overall even

20 when you account for slightly more hypotensive

21 symptoms, which consistently were judged as mild.

22   So it appears, in conclusion, and to pull

1 things together from our perspective, that in a

2 contemporary medical practice, telmisartan can be a

3 great option for preserving the benefit of the current

4 standard of care, which is ramipril in patients at

5 high risk of cardiovascular events with better

6 tolerability. Telmisartan would be expected to provide

7 increased benefit when given on top of multiple

8 therapies proven to reduce CV risk such as statins and

9 beta-blockers and aspirin in selected patients.

10   So I wish to thank the panel for your

11 patience as we've moved through these presentations

12 and for allowing us to get into the depth and breadth

13 of the database that is available, look at differences

14 of opinion and concepts regarding clinical trial

15 design. And we'll ask Dr. Friedman to come back up to

16 the podium to set the stage for our question-and-

17 answer period. Thank you very much.

18   DR. FRIEDMAN: I'd also first, just before

19 we start, like to thank some of our external

20 consultants, and this includes the list of those who

21 have not spoken but who are here with us to

22 potentially answer questions today.

1   Mr. Chairman?

2   DR. HARRINGTON: Well, thank you for very

3   nice presentations and for staying within the time

4   limits.

5   So now we have about 25 minutes before we're

6   scheduled to break. Let me open up. I'll go to

7   Sanjay, then to Ralph.

8   DR. KAUL: Thank you, Mr. Chairman.

9   The ICH 10 guidance stipulates that the

10   non-inferiority margin should be specified a priori

11   and the sponsor did that based on the only trial

12   available to them at that time, which was the HOPE

13   study.

14   It also goes on to say that it should be

15   based on both statistical reasoning and clinical

16   judgment. And because of the inherently subjective

17   nature of the latter, the choice of the margin is

18   almost always driven by statistical reasoning.

19   It also states that it should be suitably

20   conservative reflecting the uncertainty in evidence.

21   And how do we address that? I think the CBER FDA has

22   come up with a recommendation, the so-called 95/95 or

1   the 50 percent rule or the double discount, where you

2   take 50 percent discounting of the lower 95 percent

3   limit of the active control.

4   What the sponsor did was, in my estimation,

5   they under-discounted on the variance of the treatment

6   effect, which is fine. If you under-discount by just

7   taking half a standard error instead of 1.96 or two

8   times the standard error, you compensate it by over-

9   discounting on the fractional preservation where they

10 only took 50 percent.

11   So their discounting was probably closer to

12 the point estimate rather than to the lower confidence

13 limit. And that is a problem because I don't think it

14 is significant discounting or at least the spirit of

15 the guidance is not accomplished by that discounting

16 method.

17   The other statement that I had was regarding

18 to the Valiant non-inferiority margin. Yes, it is

19 right that the original medication publication

20 mentions that the non-inferiority margin was 1.13 and

21 was based on 55 percent preservation of the ACE

22 benefit based on pool estimates of the SAVED, TRACE

1   and the AIRE study. But when I actually do the

2   estimate, I get a totally different number. It's a

3   1.09.

4   We have published on this about three years

5   ago in the Annals of Internal Medicine that if they

6   had used the double discounting criteria, the non-

7   inferiority criteria would not have been established

8   in the Valiant study.

9   DR. HARRINGTON: So, Dr. Kaul, since this is

10   the question-and-answer period, do you have a question

11   that you would like to have addressed. Would you like

12   Dr. Yusuf to comment on the first? And I believe they

13   said Dr. Pfeffer was here, who is the chair of

14   Valiant.

15   Would you like them to comment on your

16   statements or --

17   DR. KAUL: Please, yes.

18   DR. PFEFFER: Thank you for the opportunity.

19   Yes, this illustrates the example of how

20   stringent the margins can be outside of the clinical

21   material. Let's go to 2002, 2000, at the time Valiant

22   was starting. And patients who coughed with an MI

1   were being switched to ARBs. And this is a real

2   event. The ACE inhibitor data was very firm. We want

3   our   high-risk patients with an MI on an ACE

4   inhibitor. The clinical situation was cough, ARB as

5   good as. Let's just do that. And if you could

6   imagine what was happening, it was any ARB and any

7   dose of an ARB.

8   The first study that came out was OPTIMAAL

9   against the ACE inhibitor captopril at the proven

10 dose. And surprise, surprise, better tolerated but it

11 did not preserve the clinical efficacy. So the

12 clinical world for a thought and for a hope was

13 switching people, and that switch was losing clinical

14 benefit. So this isn't a game. This is people were

15 actually now at greater risk.

16   Enter Valiant, large study. The margin, we

17 had many discussions here. We didn't have an open

18 discussion, but we were at the FDA many times about

19 this, before the start of the study, twice after the

20 study discussing our margin. But it wasn't just the

21 margin that won the day. Our margin, you can be on

22 one side or the other, as you just said, Dr. Kaul.

1   But it wasn't just the margin. It was what about the

2   other endpoints. What was the consistency of the

3   findings?

4   So we feel, and the FDA agreed with us, that

5   we found the dose of an ARB that preserved the

6   clinical benefit. And I think because of that that

7   helped understand non-inferiority is a synthesis, as

8   Dr. Stockbridge said, and all the aspects of our

9   synthesis in addition to the margin as was defined

10   differently. Could you imagine if we took the ICI

11   margin and didn't have Valiant and people were

12   coughing now, what would happen?

13   So I think we did the right thing back in

14   2000 whatever and took all the information available,

15   looked at the consistency of all the endpoints, looked

16   at the subgroups, looked at the on treatment, looked

17   at the margin as one aspect of it and came away with

18   the right decision.

19   DR. HARRINGTON: Dr. Yusuf, as you start to

20   respond to Dr. Kaul, I think perhaps what Sanjay's

21   getting at is both the philosophy and the math. And

22   the philosophy is something that Dr. Pfeffer just

 1   addressed, which is trying to take into consideration,

 2   as you've rightly pointed out, this is not a

 3   statistical discussion of setting of the margin; it's

 4   a clinical discussion as to what clinicians are

 5   willing to give up, so to speak.

 6   So could you perhaps comment a bit to

 7   Sanjay's question on the philosophy? But then he

 8   raises a real question about how that math is actually

 9   calculated to get us to that margin.

10   DR. YUSUF: I think the philosophy, Sanjay,

11   is just as important as one math. Remember, this is

12   one of many maths. The philosophy is we know in

13   practice when people can't tolerate an ACE, people use

14   an ARB. So can we inform them which ARBs work at what

15   dose? And that's the attempt of Valiant. That's our

16   attempt. And that's a very clinically worthwhile

17   thing. We both benefit from it as physicians.

18   I think I've in the last week preparing for

19   this spent a great deal of time reading the literature

20   and thinking. And you had done something. The ICH

21   guidelines said three things. Statistical methods

22   pre-specified, so we should only discuss what was on

1   the table before we started, not things that could

2   have been done later. The second thing it also said

3   is bring in clinical judgment. And the third is take

4   uncertainties into account.

5   Where I slightly would like to have a debate

6   with you is I wouldn't discount clinical judgment.

7   And it's just not simply a statistical exercise. It's

8   easier to talk about statistics, and therefore, if you

9   only focus on that, we're doing the field a

10 disservice.   The thing that I came across over

11 this weekend, which fits with my philosophy, is you

12 look at the totality of the evidence. I've argued

13 this in many fields. And the totality of the evidence

14 is not one endpoint, one margin, one p-value. The

15 totality of the evidence is everything in a trial that

16 matters to patients. And it may well be that in

17 future, the guidelines should say whatever margins --

18 I have no problems with 95/95. It's what you apply it

19 to. If you keep on applying it to the only one

20 endpoint and ignoring the rest, I think we're ignoring

21 a wealth of information in a trial.

22   If you use the 95/95 like if you're below

1   it, you meet it, if you jump over it, you're okay, we

2   all know that's not a very clever way of using

3   statistics. So let's use it as a continuum. How close

4   are we to it? What do the other endpoints show? What

5   does the totality of the evidence show? And if all we

6   needed was are you below or above, all we need is

7   version 1 of computers, bump, and you get the answer.

8   You don't need 12 wise people. And what 12 wise

9   people are needed for is synthesizing the evidence,

10 integrating it and putting it into a judgment.

11   This has stimulated me to work with people

12 in writing a methodological article on non-inferiority

13 trials where I think you can formalize how you look

14 for constancy. I think you can formalize how you

15 integrate information beyond your primary endpoint.

16 And in a sense, I've done it here. I've done it in a

17 formal way.

18   So, Sanjay, my answer to your point is

19 they're all valid points, but we shouldn't remain in

20 the medieval way of thinking primary endpoint, you

21 make it or not and that's the end of the story, no.

22 Let's look at the pattern of the data, the coherence

1   of the data internally, and the other supportive data

2   outside, and do they help us. So that's a longwinded

3   way of saying I agree with the statements in the ICH

4   guidelines.

5   DR. HARRINGTON: Sanjay, if you'd do a quick

6   follow-up, then I want to get Ralph and then to Bob.

7   DR. KAUL: Well, I couldn't agree with you

8   more about the primal importance of clinical judgment.

9   But we also have to acknowledge that it's rather

10 subjective. If you ask 12 wise men what is clinically

11 important, you'll get 12 different answers.

12   So I was just focusing on the math by which

13 you derived the margin. Margins based on point

14 estimate are generally discouraged, not that they are

15 not done. As an example, the GUSTO-3 used the point

16 estimate. And so margins based on point estimate may

17 be justified if the standard treatment effect has been

18 reliably and repeatedly estimated in multiple trials.

19 And if you choose a fraction preservation, it should

20 be higher than 50 percent, perhaps lower than 100

21 percent. And the theory is that the greater the active

22 control effect to be preserved, the smaller the

1 margin, the more robust the non-inferiority inference.

2   DR. YUSUF: Bob, can I just comment on that?

3   DR. HARRINGTON: Yeah, absolutely.

4   DR. YUSUF: I think what we have to say is

5 the method that we used is not just a point estimate.

6 There was a point estimate that was discounted by half

7 a standard deviation, which takes you from the 50th

8 percentile to about the 68 percentile, because the

9 distribution of a point estimate is not linear. It's

10 sort of like a Gaussian distribution.

11   The second thing was at the end of the

12 trial, the preservation on the point estimate is

13 somewhere between 95 and 100 percent and the lower

14 confidence interval, depending on which endpoint, is

15 66 to 75 percent, which meets the 50 percent sort of

16 number that Sanjay put up. So even mathematically,

17 we're not really talking of being on different

18 planets. We're talking of being around the same

19 thing.

20   Now, I want to say on the point estimate

21 discounting, after that we took the confidence, we

22 halved that for that. So there is a discounting, and

1   this is very similar to the article published by the

2   FDA on what is called the virtual comparison method,

3   I'm told. I'm not the expert, and if I'm wrong, you

4   can shut me up. But I think it is very similar,

5   although it is not as conservative as the ICIC method.

6   So it is not as non-conservative as may have

7   been seen if you only took the point estimate because

8   we discounted it twice, one half a standard deviation

9   and half the half standard deviation. And it's very

10 close to another method that uses -- so who's to say

11 which is right?

12   DR. HARRINGTON: Ralph?

13   DR. D'AGOSTINO: I had a couple of

14 questions. One was on the non-inferiority margin as

15 was just discussed. And what I was going to say, just

16 let me add to this, is that there has been a growing -

17 - I mean the idea of using the point estimate and then

18 playing with that was certainly the discussions I used

19 to hear over and over again 10 years ago. The

20 movement has been more and more in terms of the

21 confidence interval and so forth. And so I'm somewhat

22 stuck trying to figure out you're having these

1 discussions with the FDA, the field is moving, and

2 somehow or other, you're not moving with the field in

3 terms of the conservatism. I don't want to go through

4 that again; you just went through it, but the way I'm

5 looking at it.

6   The other issue I want to raise is that this

7 ONTARGET trial had three groups, and there was a

8 superiority trial comparison buried in it. Now, in

9 the materials I read and what I knew about the trial

10 and so forth, this was floating around, are we to

11 completely discount that in terms of our thinking?

12   I'm just not sure when you say look at the

13 totality, well, if you look at the totality of

14 evidence and you keep trimming out the things you

15 don't want anybody to look at, you get a different

16 view than if you look at the totality of all the

17 things that are before us and how one has to adjust

18 for multiplicity and what hypotheses were you driving

19 at.

20   So I have pulled up an example from another

21 New England Journal of Medicine that we could do,

22 where if you look at the totality and you say look at

1   the clinical sort of prospective, you end up saying

2   that diabetics who would have thought to need CABG

3   should be given revasc and those who you thought

4   should be given PCI, should be given medical

5   treatment. You can run into some very, very strange

6   conclusions if you sort of look at the consistency of

7   the data and try to bring a big picture as opposed to

8   trying to look at the formality of what did you intend

9   to and how did it unfold.

10   So could you say something about what we

11 should do with the rest of the data that's in this

12 trial?

13   DR. YUSUF: I think actually there's a

14 formal way of looking at it, and one way is to adjust.

15 And the protocol and the paper does adjust for the

16 fact that one comparison did not meet the superiority.

17 It was not found to be superior. So we had said we'd

18 use 97.5 percent confidence intervals. And most of

19 the data have shown on or around the 97.5 percent,

20 although -- and you may have noticed in some of my

21 earlier slides, I showed both the 97.5 and 95 percent.

22 They don't qualitatively change.

1   DR. D'AGOSTINO: It seemed like the drift

2 was getting to ignore and so forth. And I'm not so

3 sure that the protocol called for a splitting of the

4 alpha and so forth.

5   DR. YUSUF: It does actually. It does, and

6 we published that in our paper. And in several of my

7 slides, I gave both the 97.5, one-side at 97.5 percent

8 and the two-sided as well. And the p-values were

9 calculated for the one-sided --

10   DR. D'AGOSTINO: So this is the question.

11 If you'll look at the totality, you're telling us we

12 can discount the superiority aspect.

13   DR. YUSUF: Absolutely, absolutely.

14   DR. D'AGOSTINO: Because I don't get that

15 from what the FDA might say.

16   DR. YUSUF: Absolutely, Dr. A'gostino.

17 Yeah, that is the focus.

18   DR. D'AGOSTINO: The last question I have

19 before the break here is the consistency. I've been

20 plagued by the consistency. And are you saying -- and

21 I oftentimes will take a similar posture -- that let's

22 take a look at the hazard ratios, the relative risk,

 1   and that somehow or other captures the consistency,

 2   even though the rates are changing drastically over

 3   time.

 4   Give me an argument on -- I heard what you

 5   said. But I make that statement, but I'm not sure I'm

 6   convincing myself or anybody else when I make the

 7   statement. That says that you picked a metrics where

 8   it's consistent but the rates are changing

 9   drastically.   If you've cut MI rates by 50

10   percent somehow or other just because you maintain a

11   relative risk, are you really consistent? You may

12   wipe the disease out basically and somehow the

13   relative risk looks the same, but the drugs have

14   somehow or other lost their potency because you're

15   doing other things.

16   DR. YUSUF: Well, I think I would look at

17   that from two points of view because as a clinician, I

18   face this. When our proven ACE inhibitors work, and

19   now a new drug comes out and it works, do I reprove

20   everything that has been proven in the past all over

21   again? Well, that would lead to clinical anarchy.

22   So what do I do? I look at within the new

1   trial in people on an ACE. Say I did a new trial of

2   statin. I would look at the data two ways. In the

3   statin trials, I'd look at whether being on an ACE,

4   not being on an ACE makes a difference. And in the

5   ACE trials, I would do the flip. I would say being on

6   statin versus not being on statin makes a difference.

7   And if both of them gives me consistent results, then

8   that's giving me confidence that it really doesn't

9   matter whether my patient is on one or both, you

10   should get approximately the same result.

11   In fact, this has been the concept of the

12   polypill, as you know. The polypill is I've got four,

13   five drugs that work. If I give them together, there

14   will be a multiplicative effect. There's no evidence

15   of interactions within or across trials. So

16   generally, you should get a clinical benefit that is

17   approximately, not precisely, the summation of these.

18   So I think to the extent possible and we've done it.

19   The other way I would look at it is I'd look

20   at biology. And the way I'd look at biology is as

21   follows: if I have pharmacokinetics, I've got two

22   drugs, if one drug interferes with the bioavailability

1   of the second drug, that would worry me a whole lot

2   when I use two drugs. So as far as we know, statins

3   and ACE don't interact with each other. I'm just

4   using statin as an example. So that's another bit of

5   evidence I would take into account.

6   The third thing you said is, well, my

7   absolute event rates are going down. And to me,

8   that's not so much a sensitivity issue. It's a

9   clinical -- is the absolute benefit still clinically

10 worthwhile? That's the issue to me. And that's

11 entirely a clinical judgment when you'd say how low

12 would you go at which you stop adding more effective

13 therapies. And there you take several things into

14 account. What is the evidence for the other therapy?

15 What is the evidence for safety? So if it's an

16 intolerable drug that is expensive, even if it

17 produces a further 20 percent risk reduction, I'd say

18 well, maybe that's not worth it; whereas if my fifth

19 drug produces that 20 percent further benefit, it's

20 safe and it's relatively inexpensive, many of us would

21 say, well, that's reasonable. Let's consider it.

22   So I think you're asking a much bigger

1   question than just related to non-inferiority. And I

2   think this is where absolutely we need to bring formal

3   statistics, statistical sense as opposed to here's a

4   margin or a P-value and a great dose of clinical sense

5   and even biology into it. And that's what evidence

6   is. Evidence is not a p-value. Evidence is the

7   totality of information from diverse sources and

8   whether it forms a coherent story. And that's what I

9   think we have here. That's what I use as the yardstick

10   throughout my evaluation of evidence in multiple

11   interventions.

12   DR. HARRINGTON: Bob?

13   DR. TEMPLE: I hear a lot of terminology

14   going around and people are using things in different

15   ways, like discounting and stuff. Let me just say a

16   couple of things. I should tell you that we're in the

17   middle of writing a very long guidance on

18   non-inferiority studies at which Bob O'Neill and I

19   spend most of time. But just a couple of things

20   because I think Salim addressed all these things, but

21   I just want to be clear.

22   The fundamental requirement in a non-

1   inferiority study is that you somehow rule out loss of

2   all of the effect of the control agent. To do that,

3   you have to know what the effect of the control agent

4   is in the non-inferiority study, but of course, you're

5   not measuring it. So you have to deduce it from the

6   past. And we have been calling the margin based on

7   the effect of the drug in the past,or our best

8   estimation of what it's going to be in this study, M1.

9   When you exclude a difference greater than M1, you are

10   reasonably sure that the drug has some effect greater

11   than zero.

12   So we tend to think of that as requiring a

13   relatively high standard, roughly equivalent to the p

14   of .05 you require for a different showing trial. And

15   we don't see a great deal of flexibility on the

16   statistical analysis there. You really do have to

17   make it. The big problem, of course, is how do you

18   know without measuring it what the effect is. And

19   that goes to the question of the constancy assumption.

20   You have data from the past. You have to decide which

21   data to use, whether to use all three trials or only

22   one trial or the one that looks best in some judgment.

1 And then you have to make some decision about whether

2 you can presume the effect is still there in the new

3 trial. And Salim went into all those things where it

4 might have changed those things.

5   If you're not sure, then sometimes you might

6 say I don't think the whole effect is there, I will

7 discount it a little bit. But I totally want to

8 distinguish discounting on that basis; that is, to

9 determine what M1 is from wanting to preserve a

10 certain fraction of the effect of the control agent.

11 That is a different question, and we have been trying

12 to call the new margin based on preserving, say, 50

13 percent of it, M2. And conceptually, at least, M2 is

14 at least a little more flexible. Maybe you can take

15 into account the nature of the drug, the mechanism of

16 action, other stuff, other studies. But it's very

17 important to separate those two things.

18   So I would say, as you know from our slides,

19 we're skeptical of the M1 choice that was made here

20 because it was based largely on the point estimate

21 slightly reduced. And our inclination, which has been

22 true since we did TPA -- that was the first time we

1 did this, the so-called 95/95 -- was to say that the

2 lower bound of some analysis, a meta-analysis or

3 whatever it is, is probably where you should get M1

4 from. And then you can decide how much of it you want

5 to preserve, and there can always be a debate about

6 that.

7   But I think it's important to keep the

8 concepts separate. So one of the things I would

9 actually like to hear from Salim is why we should

10 accept the margin based on the point estimate slightly

11 reduced instead of what we thought the point estimate

12 was, even if you don't worry about constancy, which

13 was about 16 percent or that neighborhood.

14   DR. YUSUF: I think, Bob, I like your M1, M2

15 concept except your M1 is related to the point

16 estimate. So when you're trying to make what point

17 estimate are you preserving, you use the central

18 tendency in your calculation. Your second thing of

19 the M2, I think is derived from your 95/95. It's like

20 saying I've got a range of possibilities, and I want

21 to be cautious and this is it.

22   So I think the approach we took is you're

1   closer to the M1 concept. The approach, the 95/95, is

2   closer to the M2 concept. And as it happens with

3   ONTARGET, we definitely meet the M1, which is

4   preserving the point estimate, absolutely no doubt

5   about it. I don't think anybody's arguing about it.

6   And on the M2 concept on the triple endpoint,

7   depending on which margins you use, the triple

8   endpoint, it needs to unfold. On the second endpoint,

9   it's just short of it. It's not as if it's miles

10   away.

11   You and I both look at evidence as a

12   continuum, we do. So I think in this case, we have an

13   example of a trial that clearly meets M1 conceptually.

14   The second one is that it meets M2 conceptually on the

15   triple endpoint, and M2 is close on the quadruple

16   endpoint, very close but not quite on M2. So I like

17   the way you're thinking. But I think the ICIC 95/95

18   is on M2, it's not on M1.

19   DR. TEMPLE: Well, this will plainly need

20   more discussion. But our general feeling has been

21   more or less the way you say I want to be sure. When

22   you compare a drug with placebo, you don't say is the

1   point estimate different. You take the confidence

2   interval and you show that the lower bound excludes an

3   effect less than zero.

4   We have taken generally a similar position

5   by saying, well, we don't want the highest estimate or

6   a high estimate of what the effect of the control drug

7   is. We want a conservative estimate of what it is, so

8   we tend to take the lower bound. That's where we get

9   our 16 percent, which is the lower bound you get when

10 you take the confidence interval, the point estimate.

11   M2 is different. M2 is about how much to

12 preserve. It doesn't have all those other things.

13 It's how much you insist that it preserve. And

14 anyway, there'll be more discussion. But I think it's

15 crucial to do these. And it does go to how

16 conservative to be. You can make arguments that you

17 have other information, you should be less

18 conservative.

19   But the original 95/95 for thrombolytics

20 took a 25 percent reduction point estimate and said

21 the lower bound of that is 22 percent. I want 22

22 percent to be my M1, and I want to preserve half of

1 that, so I got to rule out a difference of 11 percent.

2 That's basically what they did. You can argue about

3 it. There have been debates about it. But it's

4 important to keep the concept separate, I think.

5   DR. YUSUF: Can I just add more thing, Bob?

6   You see, we know that in characterizing the

7 effects of the drug, it's not just the point estimate

8 on one endpoint and its confidence intervals; it's

9 what else it does. And I think non-inferiority trials

10 almost should get away from the concept of a single

11 endpoint in future -- I'm not talking today -- and

12 should look at all other important endpoints in making

13 these assessments. Why is that? First, patients and

14 clinicians care about all of these. The second thing

15 is we're now getting into a zone where trials are not

16 doable. And this is surprising if it comes from a

17 person like me because you know I push for bigger and

18 bigger trials throughout. And I would love to do

19 100,000 patients trials, but the danger is you're

20 going to be in a zone where you can't get the funding

21 to do it. If somebody gave me the funding, I would do

22 it, or if the regulations simplified it and said you

 1   only need three lines of data collection per patient

 2   and you can reduce your costs 99 percent, I'd love to

 3   do it. But we're not there. So realistically, if we

 4   tighten the screws on the confidence interval, there's

 5   going to be a fallout. We're not going to have a

 6   chance to test drugs.

 7   Now, equally, you don't want to have such

 8   weak standards that biocreep happens and inferior

 9   drugs get approved. So we've got to find that

10   balance. And I was thinking about it as I prepared

11   for this. And I think the balance is you do use some

12   of the general conservatism we've described. We can

13   discuss how degree of conservatism. Clearly, we were

14   conservative. The 95/95 is even more conservative.

15   But conservative on what? And is it just the primary

16   endpoint or is it several important endpoints? And is

17   the coherence of all of that relevant?

18   So it goes back to my concern non-

19   inferiority trials are hard to design, they're hard to

20   do, hard to interpret. And I think the entire

21   thinking at the FDA has been on one endpoint. I think

22   we need to be broader than that. I wouldn't put in

1   surrogates. I have big problems with surrogates. I

2   wouldn't mix in symptoms at the same time as death or

3   MI or stroke. But I think we need to think broader.

4   DR. HARRINGTON: So we're going to have a

5   lively debate, I expect, throughout the day. It's

6   10:15. Why don't we break, come back at 10:30 and

7   then we'll start with the FDA presentation.

8   (Whereupon, a recess was taken from

9   10:13 a.m. to 10:29 a.m.)

10   DR. HARRINGTON: We're going to go ahead and

11 get started. Before the break, we were going to move

12 to the FDA, but Dr. DeMets has asked permission to ask

13 a couple of questions of the sponsor. So before we

14 move to the FDA presentation, let me turn it over to

15 Dr. DeMets.

16   DR. DeMETS: Thank you. This is for points

17 of clarification. But we talked a fair amount about

18 different approaches to set the margin, whether you

19 use the point estimate or the confidence estimate.

20 But I think many of us would agree with Dr. Salim

21 Yusuf's comment that we need to use clinical judgment.

22 But I didn't hear any discussion on the clinical

```
 1   judgment from doing the math and getting a margin of

 2   .13.  And what was the clinical discussion around that

 3   was the clinically sensible thing to do or not?

 4           DR. HARRINGTON:  So the question as I

 5   understand it, David, is if we've talked about the

 6   margin being clinically meaningful, what was the

 7   discussion around the 9 versus 13 percent.

 8           DR. DeMETS:  Right.

 9           DR. HARRINGTON:  Okay.  I think somebody is

10   running to get Dr. Yusuf.  Is there somebody from the

11   sponsor who would like to comment on the discussions

12   that took place around the clinical meaningfulness

13   of -- oh, here --

14           Dr. Pfeffer?

15           DR. PFEFFER:  Well, actually, I've filled in

16   for Salim many times but not when he was in the men's

17   room.

18           [Laughter.]

19           DR. PFEFFER:  So, Salim, Dave gives us the

20   opportunity to discuss the clinical judgment involved

21   in the two aspects of margin, the more stringent or

22   less.  He wants to know what are the aspects of
```

1   clinical judgment that go into that consideration.

2   DR. HARRINGTON: I think he's pushing you

3   even a little harder. Correct me if I'm paraphrasing

4   you, David. But I think you're saying where does the

5   13 percent come from in terms of the clinician's way

6   of viewing the world?

7   DR. DeMETS: That's my point, right.

8   DR. YUSUF: That's a difficult one, Dave,

9   and I think you knew it was a difficult question.

10   I think I look at evidence as a continuum,

11   and I look at the evidence as not just based on a

12   margin. Would I have preferred this trial have 1.1085

13   or 1.05 when I started? All of you know I'm speaking

14   the truth when I say yes, I would have. But would it

15   have been practical, would this study have been done?

16   I think you all know it wouldn't have been done.

17   So the point then is, was the estimate that

18   we have sufficient to be informative clinically? And

19   as the PI, we had a lot of debates within the steering

20   committee including members of the sponsor. And we

21   said, look, if you can preserve 66 to 75 percent of

22   the benefit, isn't that good?

1   Another way to look at this is to say at the

2 end of the trial, using our one-sided confidence

3 limits, it's actually a one-sided 92 percent

4 confidence limits, the FDA's would be a one-sided 97.5

5 percent confidence limits. And of course, the results

6 could have been that we had a point estimate that was

7 quite a bit away from 1 in the wrong direction, and

8 the confidence limits would have looked worse.

9   So I think, Dave, my answer is we started

10 with something that was reasonable. Anything bigger

11 than that, I'm afraid the study would not have been

12 done. As the study was running, we did a number of

13 things to increase the power. We recruited faster, so

14 we had six more months of follow-up. We recruited

15 2,000-plus more people into ONTARGET. That helped.

16 And we increased TRANSCEND a bit.

17   Then at the end of the study, we looked at

18 the data as it happened, the results of the results.

19 And so now we are splitting hairs between what we

20 found and what the ICIC method would have liked us to

21 design it around. Is that fortuitous? Maybe. Is

22 that real? I believe likely because you look at

1 multiple events and the totality of the evidence.

2   I think like a politician, I evaded your

3 question, didn't I?

4   DR. HARRINGTON: You did very successfully.

5 So let me see if I can push you a little harder on it

6 before you sit down.

7   I think what David's getting at, Dr. Yusuf,

8 is essentially this, is that we've been asked to serve

9 as referees, if you will, in a disagreement between

10 the sponsor and the FDA. And the FDA documents tell

11 us that they asked for a 9 percent boundary, 8 point

12 something, prior to the test. You, and I appreciate

13 this dilemma, the practicality along with the clinical

14 meaningfulness, you settled somewhere out less

15 conservative for that. And now we're being asked --

16 and so it's not just considered the totality is that

17 they told you upfront they wanted 9 and you said no,

18 we're going to give you less than that. And now we're

19 being asked to referee.

20   So I think what David is trying to say is

21 pre-test, why the 13?   Was it really just a practical

22 balance along with what you thought you could

1   trade-off?

2   DR. YUSUF: I have to admit the primary

3   concern was the practical balance. But looking back,

4   I think part of it is also there was a debate. If I

5   preserved two-thirds to three-quarters of the

6   benefit -- now, remember what this is. This is you've

7   discounted it from 50 percent by half a standard

8   deviation, is about 68 percent. Is that right, the

9   statisticians? And then we went to half of that.

10   So now we are saying our study can sort of

11   be designed to ensure that about three-quarters,

12   somewhere between 66 and 75 percent, are the benefits

13   of ramipril, we can assess whether that can be

14   preserved. To us, we said, well, that's a useful

15   result. So that's a clinical judgment. And as it

16   turned out, that's the way the results turned out to

17   be.

18   I think most of us as clinicians would say

19   at least when you can't use Drug A, as long as it's

20   well tolerated, having three-quarters of the benefits

21   of a very useful drug is still worth having on a

22   cautious approach.

1   DR. HARRINGTON: Your last statement, I

2   think is something we're going to come to later today

3   about if you can't use Drug A, what might you do.

4   I don't want to get too distracted here

5   because we do want to hear from the FDA, but I

6   promised Dr. Wolf and then I'll let Dr. Temple go.

7   Emil, if it's okay, I'm going to wait.

8   DR. WOLF: This is just a little more on

9   this topic, which is Bob Temple, since I've known him,

10   which is 40 years or so, when he came here, one of the

11   things he did was encourage sponsors as much as

12   possible to come in prior to clinical trials to sit

13   down and talk about how the trial was going to be done

14   and how it's going to be analyzed. And here we have

15   on page 14 of the FDA briefing document that a meeting

16   occurred in April 10th, 2001 -- that's eight years

17   ago -- where the company said they wanted to do 1.13,

18   and the FDA said, quote, "It would be acceptable to

19   exclude one-half the excess risk associated with the

20   placebo to give an excess risk of 8.5, i.e., a 1.085

21   margin, which was 50 percent of the lower bound of the

22   95 percent confidence interval that can be allowed for

1   telmisartan compared to ramipril."

2   So given that the whole purpose of these

3   meetings between companies and FDA prior to trials is

4   to have the company do what the FDA thinks is

5   important to do and it's based on evidence, why did

6   the company not listen to the FDA? I thought that Dr.

7   Yusuf almost said about five minutes ago that if he

8   had his druthers, it would have been 1.085, or maybe I

9   heard you wrong. But whatever it was, I don't know if

10 you   were -- you probably were involved in that

11 meeting. But here you have a clear difference. And

12 in other FDA documents, they even show that the margin

13 may be properly smaller than 1.085.

14   Why did this happen? Why did the company

15 not listen to what the FDA's advice was so that here

16 we are eight years later back resolving a dispute that

17 should have been settled then? The company should

18 have done what the FDA asked. I don't understand

19 this.

20   DR. HARRINGTON: And this is part of your

21 question as well, Dr. DeMets.

22   DR. DeMETS: Right.

1   DR. HARRINGTON: Okay. So this is a really

2   key one for us to --

3   DR. YUSUF: I think, Dr. Wolf, I don't wish

4   to imply that I clearly preferred 1.085 versus 1.13.

5   Those people who know me prefer that my approach to

6   trials is do the largest trial possible. And

7   practically in every field, our group has tried to do

8   it. There are two or three groups that try to do it.

9   But I look at evidence as a continuum, not

10   as a yes or no. If I can't get the perfect trial, I

11   try to get as close as possible to it. So to me, 1.13

12   was not as it was a bad trial, 1.13 is still a very

13   good trial. And mind you, it's not based on just the

14   point estimate. It's discounting the point estimate,

15   then halving it. So there is a substantial amount of

16   discounting going on.

17   What the FDA requested was even more

18   conservative in design and is practical. And the

19   practicality is it would have doubled the study size,

20   and obviously, essentially doubled the study cost.

21   That just wasn't practical then. And even today, I do

22   not know of a study of five-year durations with a drug

 1   of 55,000 people. It's just not practical.

 2   We can keep on tightening the screw and say

 3   do bigger and bigger studies. It just is not

 4   practical. And I've done about 50 major trials,

 5   collectively over a half a million people. I care

 6   about getting the right answer. And if we start to

 7   make the standard so difficult, I think many of us

 8   will find we can't find the right answer. So that's

 9   one side of it.

10   The other side of it is whatever you decide

11   on 1.13 and 1.085, really these are relatively small

12   differences. They aren't the differences that is half

13   a world apart. They're quite small differences. At

14   the end, our confidence interval one-sided is 92

15   percent. The FDA's is 97.5 percent one-sided. In the

16   end, the data speak to it. It's not what you started

17   off; it's what you ended up with. And in the end,

18   it's all the evidence that comes to it.

19   So I think it would be a mistake for any of

20   us in the room to say that I can defend one

21   non-inferiority margin versus another non-inferiority

22   margin. It isn't a gold standard. And my

1 understanding of discussions with FDA, and I've been

2 in several before the study and in the study, is

3 discussing what the issues are rather than, as you

4 said, do what the FDA tells you. I don't think that's

5 the tone. I don't think Bob Temple or Norman

6 Stockbridge ever intended that to be. They can

7 correct me.

8   So I think what the sponsor and what the

9 study did was reasonable, not as conservative as the

10 FDA would have liked, but it was reasonable.

11   DR. HARRINGTON: Okay. I'm going to let Bob

12 speak. And then I know, Jonathan, you do want to

13 bring in perhaps the industry perspective here, so

14 I'll let you do that.

15   DR. TEMPLE: Of course, I'm as horrified as

16 Sid is when we suggest something and people don't take

17 our advice.

18   [Laughter.]

19   DR. TEMPLE: But leaving that aside, I still

20 want to remind everybody that on the question of

21 whether the drug has any effect at all, M1, it really

22 doesn't matter whether you use theirs or ours because

1 they're lower than 16, unless you're worried about

2 constancy. Because when we met with them, we said,

3 yes, you can assume that the control drug has an

4 effect of about 16, that ruling out 16 percent would

5 mean there's still some effect. We want you to

6 preserve half of it. You will hear there's some

7 doubts raised about whether that 16 percent is still

8 good in light of other data. I'm not trying to

9 address that.

10   I wanted to actually go to Dave's question.

11 We have in an informal way, sort of said, in these

12 large trials preserving -- ruling out a loss of more

13 than 50 percent is generally the best you can hope

14 for. That first came up with thrombolytics where

15 actually this advisory committee in its previous

16 iteration said 50 percent? Come on, this is death.

17 You got to retain 75 percent of it. And we did the

18 calculations. That would have taken a study of over

19 55,000. And so -- this was CBER; we had nothing to do

20 with it -- they said 50 percent will have to do.

21   I just wondered whether you're now nervous

22 about that, David, because that is the standard that

 1 is reliably being enunciated at least most of the

 2 time. There could be exceptions, and it's not written

 3 in stone. But we're generally saying that if you rule

 4 out at our usual significance level a loss of 50

 5 percent, that probably is good enough. It's worth

 6 remembering that to do that, you almost have to be

 7 identical in practice.

 8   But are you now worried about that? Because

 9 that's become fairly standard in hundreds of

10 discussions that we're having.

11   DR. DeMETS: Well, as some of you know, I

12 have been worried about the whole non-inferiority

13 paradigm from basic assumptions and on forward. It's

14 just if you woke me up in the middle of the night and

15 said how much are you willing to give up to take a new

16 therapy on an endpoint like death, MI and stroke, I'd

17 be pretty fussy, all things being equal.

18   DR. TEMPLE: I guess my question comes to

19 this. When you say my drug is effective at a p of

20 .05, we look at the point estimate to try to figure

21 out what the drug actually does. But of course,

22 that's not what we've shown. What we've shown is it's

1 better, slightly better, ever so slightly better than

2 nothing at all.

3   This is a little analogous to that. What

4 we've been telling people is you got to rule out, with

5 a high degree of statistical rigor, a loss of 50

6 percent, but I don't think anybody believes that's

7 likely to be the true effect anymore than people

8 believe when you do a study and show a p of .05 that

9 the effect is barely better than zero. That's why we

10 look at point estimates.

11   So how do you reconcile that?

12   DR. DeMETS: I don't want to distract this

13 conversation right now. But the point estimate we

14 tout is a point estimate of something that is an odd

15 population. It's the volunteers that showed up. So

16 we put a lot of weight on those. We haven't always.

17 But in fact, it's a funny estimate, right? And we put

18 a confidence number on it. We don't really know what

19 it is, but we know it's better than zero, at least we

20 believe that.

21   Then we start using that number as it was

22 really precise, and then putting confidence levels

1 around it and taking half of it, I'm getting very

2 nervous about as we move down that path, quite

3 frankly. I don't have a better --

4   DR. TEMPLE: I mean the alternative is to

5 show superiority always.

6   DR. DeMETS: Well, we all love that, but

7 that's not real life, right?

8   DR. HARRINGTON: Jonathan, last comment

9 before we move to --

10   DR. FOX: Thanks very much, Mr. Chairman.

11   Just a general comment around Dr. Wolf's

12 point. Certainly sponsors -- well, I would say, in

13 general, people should notice that even Dr. Temple

14 used the word "advice." The so-called requirements

15 for registration and for passing certain bars are

16 labeled as guidances for industry. So I'm not aware

17 of any legislation or requirement that sponsors follow

18 the FDA's advice. But I would agree with Dr. Wolf

19 that, in general, sponsors should listen very

20 carefully to what the agency proposes that they

21 consider doing.

22   Having said that, at the time this trial was

1   designed and initiated, as the sponsor's pointed out,

2   a lot's happened in eight or 10 years. And the amount

3   of information they had available to them at the time

4   was a bit more limited. And it was also clear, I

5   think, there were a number of trials that were just

6   getting under way and everyone could expect there to

7   be a lot more information emerging in the years hence.

8   So you could view it as the sponsor

9   maybe -- I think Professor Yusuf's point about

10 practicality coming into the mix and making some

11 internal decisions -- the sponsor has explained about

12 how they decided to take their program forward -- may

13 be taking a bit of a gamble, if you will, on what

14 additional information might emerge in the years

15 during which a trial was running, that might then

16 influence the dialogue that the agency might have with

17 the sponsor.

18   So the point I wanted to make really is that

19 it's not quite as cut and dried as you must do what

20 the agency asks you to because the agency doesn't

21 really tell you to do anything; they advise. And, in

22 general, I recommend that we follow the agency's

1 advice, but it's not required.

2   DR. HARRINGTON: Fair comment.

3   Let's turn now our attention to both the

4 clinical and statistical review of the data by the

5 FDA.

6   DR. U: Good morning, Mr. Chairman and

7 members of the advisory committee and representatives

8 from the pharmaceutical industry and the academic

9 institutions, representatives from the public citizen

10 groups, FDA colleagues, ladies and gentlemen, this

11 morning Dr. Zhang and I will present our review

12 findings on this new efficacy supplement for NDA

13 20-850, my colleagues. We'll present like this. I'll

14 present first the superiority analysis. Then Dr.

15 Zhang will explain the statistical considerations we

16 have about the non-inferiority analysis. Then I come

17 back and discuss the clinical trials that were in the

18 literature and how we intend to look at it.

19   So this efficacy supplement was submitted

20 for the indication of production in the risk of

21 cardiovascular death, myocardial infarction, non-fatal

22 stroke or heart failure hospitalization in a

1 population of patients who are 55 years or older and

2 at high risk of developing a major cardiovascular

3 event.

4   The sponsor submitted three trials, ONTARGET

5 as the pivotal trial and TRANSCEND and PRoFESS as the

6 supplemental trial. Now, this morning the sponsor has

7 made a very detailed presentation about the enrollment

8 criteria, the design, the results, and I won't go back

9 into them. I'll just briefly describe the salient

10 points that are relevant to our discussion.

11   Now, ONTARGET was a large trial of over

12 25,000 patients who are at high risk of major

13 cardiovascular event. And they were enrolled into

14 three treatment arms, telmisartan plus ramipril

15 combination therapy, telmisartan monotherapy or

16 ramipril monotherapy. And they were followed for

17 about an average of four and a half years.

18   The primary endpoint was a composite of

19 4-components, cardiovascular death, non-fatal MI,

20 non-fatal stroke and heart failure hospitalization.

21 And there was a secondary endpoint, which is a

22 composite of cardiovascular death, MI and stroke,

1 which is similar to the HOPE trial, which is the

2 historical ramipril trial that we'll be talking about

3 for the non-inferiority analysis.

4   The ONTARGET trial was intended to show the

5 superiority of the combination of telmisartan plus

6 ramipril over ramipril and the non-inferiority of

7 telmisartan versus ramipril. Then we'll come to the

8 first supportive trial, which is the TRANSCEND trial.

9 That trial randomized about 6,000 patients who are

10 also at high risk of a major CV event. The difference

11 is that they are intolerant to ACE inhibitors and they

12 don't have significant proteinuria.

13   Now, there are many publications in the

14 literature about the CV risks, event rates that occur

15 in ACE intolerant patient versus tolerant patient. We

16 won't go into that, but roughly to say that these are

17 also patients with high risk, CV high risk, almost

18 similar to ONTARGET, though not absolutely.

19   They are followed for four years, eight

20 months. And the intent of the study was to show

21 superiority of telmisartan over placebo for the same

22 4-component endpoints in ONTARGET. This study also

1   has a secondary endpoint of 3-components; that is, CV

2   death, MI and stroke, similar to the HOPE trial.

3   Then we have the last trial, the PRoFESS

4   trial, which is the very last trial of about 20,000

5   patients in a different population. These are

6   patients who had had an ischemic stroke in the last

7   four months or so and are now clinically stable,

8   neurologically stable. And they were randomized to

9   receive either placebo or telmisartan and followed for

10   two and a half years. This is a shorter trial.

11   The endpoint here is different.   The

12   primary endpoint is the time to the first recurring

13   stroke. The secondary endpoint was to find almost a

14   4-fold,   4-component endpoint like in ONTARGET, CV

15   death, MI, stroke and heart failure hospitalization.

16   It doesn't have a 3-component endpoint specified in

17   the protocol, but we analyzed the two so as to compare

18   these three trials across the board. The study also

19   is intending to show superiority of telmisartan over

20   placebo.

21   Now, we did an intensive review of both

22   safety and efficacy components of the submission. But

1   for this morning, we are going to confine our

2   discussion only to the efficacy review.

3   Just to remind you that we have the HOPE

4   trial as a historical trial with 3-component endpoint

5   and ONTARGET trial, which is the current trial with

6   the composite of 4-components, the only difference

7   being the heart failure hospitalizations.

8   Now, going back to the historical HOPE

9   trial, we have the HOPE data in-house, so we went back

10 in the time to first hospitalization and re-analyzed

11 the HOPE data for the 4-component endpoint.

12   So this is the 3-component endpoint, which

13 is the pre-specified primary efficacy endpoint in

14 HOPE. And there's a technically significant reduction

15 in relative risk by 22 percent. The 4-component

16 endpoint also shows an almost similar beneficial

17 effect. So the HOPE trial, we think is a powerful

18 trial at that point in time with the patients and

19 treatment available and show powerful results.

20   How about ONTARGET? With ONTARGET, we found

21 that for both the primary 4-component endpoint and the

22 secondary 3-component endpoint, the telmisartan plus

1   ramipril combination is not superior to ramipril

2   monotherapy. And this is for the intend to treat

3   population. We checked the -- population. It showed

4   similar results. We also analyzed and accounted for

5   the patients with heart failure documented with x-rays

6   for pulmonary congestion. We also accounted for the

7   baseline systolic blood pressure, the change in

8   systolic blood pressure over time and the systolic

9   blood pressure at the last visit prior to a primary

10 event. And all of them showed the same thing, that

11 telmisartan plus ramipril is not superior to ramipril

12 monotherapy.

13   In fact, if we look at these hazard ratios,

14 either 1 or .99, it's almost like telmisartan plus

15 ramipril is identical to ramipril. And the p-values

16 are also approaching 1.

17   I would like to look at this in a different

18 light. We can think of this trial also as a trial of

19 telmisartan versus placebo, and everybody who is

20 getting ramipril, and then it shows that telmisartan

21 is not superior over placebo in ONTARGET.

22   In TRANSCEND, the telmisartan again is not

1 superior to placebo for the 4-component endpoint. For

2 the secondary 3-component endpoint, it looks there is

3 a marginally significant p of .048. However, please

4 remember, one, that the primary endpoint failed

5 already. So the sponsor has used up all of the alpha,

6 so you can't go on -- if I'm strict reg reader, you

7 can't even go and analyze the secondary endpoint. And

8 also, please remember that this p of .048 is full

9 adjustment. After we adjusted this for multiple

10 comparison, it's no statistically significant. So the

11 TRANSCEND is another failed trial comparing

12 telmisartan to placebo.

13   Then we go to PRoFESS. The PRoFESS trial

14 fail for these pre-specified primary endpoint

15 regarding stroke. We evaluated for the secondary 4-

16 component endpoint, and it fails to show superiority

17 of telmisartan to placebo. And a post-op analysis of

18 the 3-component endpoint also shows that telmisartan

19 is not superior to placebo.

20   So if you put the total list of what

21 everybody seems to be using this morning, the totality

22 of evidence, if we took the total evidence on three

1   very large clinical trials, it shows that ONTARGET,

2   which we consider as the comparison of telmisartan to

3   placebo in everybody who is getting ramipril, failed

4   for both the 3-component and the 4-component endpoint.

5   And both the TRANSCEND and PRoFESS trial also failed

6   for the the 3-component and 4-component

7   endpoint -- shows that the marginal p-value we found

8   is not statistically significant after adjustment for

9   multiple comparisons.

10   So we are faced with a totality of three

11   failed large trials. Do we even need to go ahead and

12   look at the non-inferiority analysis when we know

13   that -- or when we have found that telmisartan is not

14   shown to be beneficial over placebo? Now, that is the

15   question I think we have to wrestle during the

16   afternoon during our discussions. But we are now a

17   kinder, gentler FDA. We look at all of the evidence

18   they submitted.

19   [Laughter.]

20   DR. U: So I'll ask Dr. Zhang to present the

21   statistical consideration of non-inferiority analysis

22   in the ONTARGET. And we'll have a lot of discussion

1 in the afternoon about this and other aspects that

2 will come up.

3   DR. ZHANG: Before I start on my part of the

4 presentation, I'd like to say that I agree with

5 Professor Yusuf, that the non-inferiority analysis is

6 not only a statistical exercise. So that's why Dr. U

7 and I are doing a joint presentation today because we

8 feel we cannot separate our presentations. And at one

9 point, we even think about standing side-by-side at

10 the podium. So let me spend a few minutes to lay out

11 the concept of non-inferiority tests and the issues

12 that we encountered during our review.

13   Using hazard ratio as an example, T stands

14 for treatment and C stands for active control. So if

15 the hazard ratio equals 1, that means the treatment is

16 about the same to active control. And if the hazard

17 ratio is below 1, that means the treatment is more

18 efficacious than active control. And if hazard ratio

19 is above 1, that means active control appears to be

20 better than treatment.

21   So if a trial has a hazard ratio estimate

22 with a confidence interval like this with the upper

1   bound below 1, we say the treatment is superior to the

2   active control. Now, M is a non-inferiority margin if

3   it's defined and pre-specified. M is always greater

4   than 1. So if the upper bound of the confidence

5   interval is below M, we say the treatment is

6   non-inferior to the active control.

7   On the other hand, if we look at the lower

8   bound of the confidence interval, if it's above 1,

9   then the treatment is inferior to the active control.

10 Of course, if the confidence interval covers 1 and M,

11 it's inconclusive.

12   So even as early as April 2001, there was

13 disagreement between FDA and the sponsor on the

14 non-inferiority margin, as you heard from the

15 sponsor's presentation early this morning. The

16 sponsor proposed non-inferiority margin as 1.13, and

17 the FDA reviewers calculated a non-inferiority margin

18 as 1.08. But people saw the number 1.085, so I just

19 want to clarify that at the IND stage, the non-

20 inferiority margin was computed based on the

21 confidence interval only was two decimal point

22 precision. And I calculated following the same exact

1 method with the patient level data.

2 So it's more precise. It should be 1.082. And that's

3 the only difference. But for my presentation, I'll

4 just use 1.08.

5   So here I'm going to explain how we come up

6 with the margin. R is ramipril, P is placebo. In

7 order to test the non-inferiority of telmisartan over

8 ramipril, we need to look at the treatment effect of

9 ramipril in historical trials. We used only the HOPE

10 trial in deriving the non-inferiority margin. This is

11 because the HOPE trial was the only ACE inhibitor

12 trial in such patient population at that time.

13   As you can see, the hazard ratio of ramipril

14 over placebo, the point estimate is .78. And this

15 means an estimated 22 percent risk reduction in

16 ramipril group in the HOPE trial. And we invert that

17 number to get 1.29. This is the risk increase in

18 placebo group. So, basically, it's saying being on

19 placebo has 29 percent of risk increase compared to

20 being on ramipril in the HOPE trial.

21   Now, basically, if telmisartan is compared

22 to ramipril, this is how much worse it can get but

1 still better than placebo. So that's why we need to

2 invert the number. Note that this is only the point

3 estimate. And in reality, we do not know the true

4 treatment effect of ramipril. So we quantify the

5 uncertainty of the point estimate by using confidence

6 intervals. And often, we take the variability of the

7 estimate into account and use the lower bound of 95

8 percent confidence interval. In this case, it's 1.17.

9 And on top of that, we take half of the distance to

10 unity to get 1.08. This is to retain 50 percent of

11 the treatment effect of ramipril and to make

12 sufficient assurance that when telmisartan wins non-

13 inferiority, it has a clinical meaningful effect.

14   So the sponsor's margin of 1.13 also derived

15 based on HOPE trial only. But instead of using the

16 lower bound 95 confidence interval, they discount the

17 point estimate of 1.29 to 1.26. As you heard the

18 explanation, they also take half of the distance to

19 unity to get 1.13.

20   Now, this table shows the result for

21 non-inferiority tests in the 4-component and

22 3-component composite endpoints in ONTARGET trial.

1 The 4-component endpoint is a primary endpoint. The

2 3-component endpoint is a secondary endpoint. As you

3 can see, the upper bound of the 4-component primary

4 endpoint is 1.10. This is above the FDA's

5 non-inferiority margin, but below the sponsor's

6 non-inferiority margin.

7 　　　　　Here, we only look at 97.5 percent

8 confidence interval. This is because there are two

9 comparisons for the primary endpoint, the superiority

10 test of combination of telmisartan plus ramipril over

11 ramipril and the non-inferiority testing of the

12 telmisartan versus ramipril. So by multiplicity

13 adjustment, we look at it a 97.5 percent confidence

14 interval.

15 　　　　　The 3-component secondary endpoint has an

16 upper bound of 1.08. And here are some questions we

17 had during our review. There appear to be three

18 relevant historical trials, HOPE, EUROPA and the

19 PEACE. These are the ACE inhibitor trials in patient

20 population with CV risk factors. And Dr. U is going

21 to provide you more detailed information about these

22 three trials later on in his presentation and also

1 tell you why we only considered these three trials.

2   So the non-inferiority margin in ONTARGET

3 trial was derived based on HOPE trial only. As I

4 mentioned, that was the only available ACE inhibitor

5 trial in such patient population at that time. So as

6 over the years, EUROPA and the PEACE become available,

7 should we look at all the available new trials and

8 derive a new margin or we need to base it on HOPE

9 trial only? Also, there appears to be some

10 heterogeneity amongst the three trials. So if we were

11 to include new trials, should we use all three

12 available trials or we include two trials? And if

13 only HOPE trial is used, should we use 95 percent

14 confidence interval or 99 percent confidence interval,

15 which I'll talk in a little more detail in the next

16 slide.

17   The second question is, is the constancy

18 assumption valid? Well, in non-inferiority tests, it

19 seems the placebo arm is absent. So we're relying on

20 a critical assumption that the effect side of active

21 control remains the same in a non-inferiority trial as

22 it was in the historical trials. But as the standard

1 care in clinical practice evolves, we are not sure

2 whether the constancy assumption is valid.

3   So we performed some exploratory analysis to

4 look at the effect of ACE inhibitor to see whether it

5 varied by baseline covariates. The baseline

6 covariates in all these trials are different. So for

7 example, more patients are taking beta-blockers and

8 lipid-lowering agents nowadays. So could the

9 variation explain the change of treatment effect size?

10   Usually, we take 95 percent

11 confidence -- the lower bound of 95 confidence

12 interval as a conservative estimate for the treatment

13 effect of the active control. Now, because we only

14 use HOPE trial to derive the margin, the inter-trial

15 variability cannot be assessed. So should we use 99

16 percent confidence interval in this case? And many

17 actually argued about that. As you can see from the

18 slide, the   non-inferiority margin based on

19 99 percent confidence interval is slightly more

20 conservative than the 95 percent, the one based on 95

21 percent confidence interval.

22   So we also look at the non-inferiority

1   margin derived based on all three available trials,

2   HOPE, EUROPA, and PEACE. Depending on which model we

3   use, the margin varied from 1.04 to 1.07. And we used

4   both fixed effect model and the random effect model.

5   The fixed effect model basically assumes the true

6   treatment effect from all those three trials are

7   identical, and the random effect model assumes the

8   true treatment effect of the active control from these

9   three trials came from the same distributions. So it

10 allows the inter-trial variability to build into the

11 model.

12   And we also look at the non-inferiority

13 margin based on the HOPE and EUROPA trials. This is

14 because we find some heterogeneity in the PEACE trial.

15 So we exclude the PEACE trial and look for only two

16 trials and derive the margin.

17   Now, the sponsor proposed a margin of 1.13.

18 And based on our analysis, the margin should be

19 somewhere between 1.03 to 1.08. And the upper bound

20 of the 4-component composite endpoint in ONTARGET

21 trial is right between 1.08 and 1.13.

22   So I'd like to point out that the secondary

1 endpoints cannot be validly analyzed if the primary

2 endpoint fails. As we recall, the 4-component

3 composite endpoint is the primary endpoint for

4 ONTARGET and TRANSCEND. It failed for the superiority

5 test in TRANSCEND. It failed for the superiority test

6 in ONTARGET. It would also fail if we used a margin

7 of 1.08 for the non-inferiority test. So we cannot

8 have a valid inference for the secondary endpoint,

9 which is 3-component composite endpoint even though

10 it may show some nominal significance.

11   So here is a graph showing the hazard ratio

12 of all three trials. As you can see, there appears to

13 be some differences in effect size from HOPE to EUROPA

14 and in PEACE trial. And HOPE appears to have the

15 largest treatment effect.

16   So why does the constancy assumption matter?

17 Well, in ONTARGET trial, since the placebo arm is

18 missing, we cannot directly assess the ramipril effect

19 in ONTARGET. Instead, we look into the historical

20 trials to compute the ramipril effect. So assume here

21 is the ramipril effect in HOPE. Now, if the ramipril

22 effect in ONTARGET trial is the same as it was in

1 HOPE, then we can derive this margin M based on HOPE

2 trial. But what if HOPE trial shows the best result

3 and the ramipril effect in ONTARGET is smaller? Then

4 the margin ought to be more conservative then it

5 should be in the first case.

6   So basically, the validity of the

7 non-inferiority test solely relied upon the accuracy

8 of assumed effect on the active control. And the

9 issue is we do not know whether the ramipril effect

10 has reduced. And if it has reduced, what is the

11 magnitude? And if a margin is chosen too large, a

12 seemingly successful trial would have given you some

13 erroneous conclusion.

14   In addition, we explored the impact of some

15 clinical covariates on ACE inhibitor effect. Well, in

16 essence, various covariates do not seem to effect much

17 the treatment effect. Well, one possible exception we

18 find is the use of anti-platelet drugs in HOPE trial.

19 The ACE inhibitor effect appears to be smaller in

20 patients who took anti-platelet drugs.

21   Now, I'd like to say that due to the small

22 sample size in some of the strata -- for example, only

1   3 percent patient in EUROPA had a previous history of

2   stroke or TIA, so the confidence interval is extremely

3   wide in those cases. And for some covariates, we do

4   not know whether the treatment effect is truly

5   indifferentiable.

6   So here I just show you an example of the

7   hazard ratio stratified by each clinical covariate in

8   HOPE trial. And as I mentioned, we find that the

9   anti-platelet make an impact on the treatment effect.

10 The patient who did not take anti-platelet drugs

11 seemed to benefit much more from ramipril compared to

12 patient who took anti-platelet drugs. But this effect

13 did not show in the PEACE trial and is not clear in

14 the EUROPA trial.

15   So now I'll pass back to Dr. U to continue.

16   DR. U: Thank you, Dr. Zhang.

17   As you've heard from Dr. Zhang, it looks

18 like the ACE inhibitor effects appears to be

19 diminishing from HOPE to EUROPA to PEACE. Now,

20 earlier this morning, I think you heard Dr. Yusuf

21 saying that these appear to remain the same with the

22 whole host of clinical trials that were shown in his

1 meta-analysis. And I respect it very much.

2   But my opinion is these trials, some of

3 these are -- let's see, the SOLVD in the population of

4 patients with heart failure and then SAVD, TRACE,

5 AIRE, (unclear). These four trials are in a

6 population of patients who are post-MI, so they tend

7 to have different risks. They tend to have larger,

8 more (unclear) and they tend to be able to show the

9 effect of ACE inhibitor. So you cannot use these and

10 lump them together with the ACE inhibitor tasks in

11 patients who are at high risk but not in heart

12 failure, the so-called Stage A or maybe B heart

13 failure that we are seeing in HOPE, EUROPA and PEACE.

14 And believe me, I like to look at the earlier trials.

15 I did my first clinical trial in 1972 so that shows my

16 age. And looking back at the HOPE, EUROPA and PEACE

17 trial, we have the data in-house for HOPE and EUROPA.

18 I was the reviewer for the EUROPA trial, and we are

19 very fortunate to have Dr. Pfeffer provide us with the

20 PEACE data. So we looked at this data.

21   In the HOPE trial, the population of patient

22 comprises people who are 35 years or older with a

1   history of coronary artery disease or peripheral

2   vascular disease or diabetes plus a CV risk factor

3   like hypertension or elevated cholesterol or cigarette

4   smoking, et cetera. So HOPE trial enrolled a larger

5   number of patients who have relatively lower sort of

6   cardiovascular risks than compared to EUROPA or PEACE.

7   In EUROPA or PEACE, patients had to have in

8   EUROPA a 70 percent narrowing of more than one major

9   coronary artery or a serious coronary artery disease

10 as documented by a MI three months before, or

11 revascularization would have been six months before.

12 And if they had chest pain history, they had to have a

13 positive ECG or echo or nuclear stress test. So the

14 EUROPA is most stringent in that it has to have

15 documentary evidence to confirm the risk status.

16   In PEACE, too, a patient has to have a

17 documented MI, automatic CABG or PTCA or you can have

18 evidence of more than 3 percent obstruction in at

19 least one vessel. And they went further. In PEACE,

20 the patient has to have a left ventricle ejection

21 fraction of more than 40 percent by contrast or

22 radionuclide, ventriculography or echocardiography and

1 normal left ventricle wall motion. So these are

2 patients at high risk but without left ventricular

3 function or structural anomaly.

4   All three trials enrolled large numbers of

5 patients. In HOPE, there was 9,000 patients, EUROPA,

6 12,000 and PEACE, 9,000. And all three trials used

7 the high dose of ACE inhibitor, ramipril 10 milligram

8 per day or perindopril 8 milligram per day or

9 trandolapril 4 milligram.

10   Now, in the PEACE, looked at the literature

11 review, there was a discussion that said that about

12 half or only half or more of the patients are at this

13 dose because of some reason with patient not

14 tolerating this. And that may be partly the reason

15 why the PEACE trial failed to show a positive effect.

16   They were all followed up for four years or

17 4.8 years, so these were long-term trials. In the

18 HOPE trial, the composite endpoint was cardiovascular

19 death, MI or stroke. For EUROPA, it was CV death, MI

20 or coronary arrest with a successful resuscitation.

21 And then in PEACE, additionally, the endpoint was

22 cardiovascular death and MI and later the endpoint of

1   CABG and PCI was added in.

2   Now, that may have been a little bit

3   difficult for analysis because CABG and PCI procedures

4   sometimes depend on whether the cardiologist or the

5   hospital wants to do it or is able to do it. So this

6   dependent on physician preference, and that may also

7   be one of the reasons which confounds the analysis for

8   PEACE and the reason why it may have failed.

9   As we all know, the HOPE trial was stopped

10   six months earlier because of overwhelming effect.

11   Now, in the HOPE trial there is a 22 percent reduction

12   in CV death, MI and stroke. And that is maintained

13   when we also analyze it for a 4-component endpoint and

14   in the heart failure hospitalization. So as we said

15   earlier this morning, the HOPE trial is a powerful

16   trial. It gives consistent results whether we look at

17   one endpoint or two endpoints or four endpoints or

18   three endpoints and look at all this effects.

19   Now, in EUROPA, too, for its own

20   pre-specified endpoint, there was a 20 percent

21   reduction in CV death, MI and cardiac arrest with

22   successful resuscitation. But when we look at the

1 HOPE endpoint, it still shows a 17 percent reduction,

2 which is statistically significant. But nevertheless,

3 this has reduced from the effect size of HOPE. In

4 PEACE, there's only a 7 percent reduction in the HOPE

5 endpoints, and this is not statistically significant.

6 So what this will try to consider what could be the

7 reason for this probably showing a little bit of

8 reduction or appearance of a decrease in effect size.

9   If we look at these three trials,

10 considerably larger proportion of patients in the

11 EUROPA and the PEACE have patients who are on anti-

12 platelet drugs, more patients on beta-blockers, more

13 patients on lipid-lowering drugs and more patients at

14 baseline who had had coronary revascularization

15 procedure at baseline. And these probably can reduce

16 the endpoints events, the outcome events.

17   Also, PEACE and EUROPA had fewer patients

18 who are stroke or TIA and diabetes, and these two may

19 have contributed to a smaller effect size than we see

20 with EUROPA and PEACE compared to HOPE.

21   Now, going on to ONTARGET and TRANSCEND, we

22 did the same analysis, same comparison. It looks also

1   like that the patients in ONTARGET and TRANSCEND have

2   a larger proportion of people who are on beta-blockers

3   and lipid-lowering agents, which would have reduced

4   the effect size to a certain extent. And also, fewer

5   patients who have angina, stable and unstable, in

6   ONTARGET and TRANSCEND compared to HOPE, this, too,

7   has reduced the effect size.

8   On the other side of the coin, we had more

9   patients with stroke and TIA and hypertension in

10 ONTARGET, which could have balanced the effect. And

11 overall effect, we don't know. But what we now know

12 is that we could not find the superiority or

13 non-inferiority using our FDA margin, probably because

14 of the differences in the concomitant therapy,

15 differences in the patients' status at baseline. And

16 that question concerns the assumption.

17   What has happened is that these are the

18 annualized event rates in the placebo group. In

19 TRANSCEND, the annualized placebo rates were 75

20 percent or less than that in HOPE. So that is also

21 another finding that tells us that there may be a

22 difference in constancy assumption.

1   So with this information and background, we

2   think that if we are going to test for telmisartan

3   versus ramipril, then we should use our relatively

4   conservative NI margin. And the reason, as we stated

5   before, is that there's been apparently diminishing

6   ACE inhibitor effect from HOPE to the subsequent

7   trials. There have been uncertainty in constancy

8   assumption. And then using HOPE alone, we could not

9   estimate the inter-trial variability. And for this

10   reason, we would like to suggest that a conservative

11   module should be used. How conservative, please is

12   for the advisory committee to tell us, I think. And

13   this is in the background of our finding that

14   telmisartan is not superior to placebo in three large

15   trials.

16   So to conclude, we found that ONTARGET

17   trial, that's not the most superiority of telmisartan

18   plus ramipril combination over ramipril. And

19   TRANSCEND and PRoFESS trials do not demonstrate

20   superiority of telmisartan over placebo. And the

21   totality of these superiority analysis is that all

22   three trials fail.

1   Looking at ONTARGET as a comparison of

2   telmisartan versus placebo in all patients who are

3   receiving ramipril and also considering the fact that

4   the 3-component in TRANSCEND, which has a marginal

5   p-value, is no longer statistically significant when

6   it is adjusted for multiple comparison.

7   So in the face of these three large trials

8   that have failed to show superiority of telmisartan

9   over placebo, should we still test for non-inferiority

10 of telmisartan to placebo? If we do, then we think

11 that the non-inferiority test should be done with a

12 margin of 1.08 or less, in which case ONTARGET does

13 not demonstrate non-inferiority of telmisartan to

14 ramipril. And as I stated before, the reason appears

15 to be because there is a diminishing ACE inhibitor

16 effect. There is a change in clinical practice, which

17 may have changed the constancy assumption.

18   Finally, we would like to thank our review

19 team who helped us throughout the process and in the

20 presentation and the preparation of the presentation.

21 Thank you very much.

22   DR. HARRINGTON: Thank you. That was a very

 1 helpful presentation.

 2   I'll start with Ralph, go to Sanjay.

 3   DR. D'AGOSTINO: I have a couple of

 4 questions. One question is that when you look at this

 5 ONTARGET and you study and you use it as a

 6 placebo-controlled trial, isn't that quite unfair?

 7 It's a combination that you're dealing with, and the

 8 combination in terms of beating out individual

 9 ingredients doesn't necessarily tell you what it would

10 do against a placebo. Both ingredients could beat out

11 a placebo, but the combination could beat out either

12 of the two components. So I'm not sure I follow the

13 argument that we can look at that as a placebo trial.

14   DR. HARRINGTON: So let me just rephrase it,

15 Ralph, so that one of the cases that was made was that

16 T plus R is not better than R, is not the same as T

17 plus R is not better than R plus placebo.

18   DR. D'AGOSTINO: T is better than placebo.

19 T may still be better than placebo, but T plus R may

20 not be better than T or R.

21   DR. HARRINGTON: Bob or Norm, do you want to

22 comment on that?

1   DR. TEMPLE: Well, I agree with that. I was

2   whispering that to Norm, too. So there are two trials

3   that failed to show it, but I wouldn't count that.

4   That's a different question.

5   DR. D'AGOSTINO: Then another question I

6   have in terms of the constancy. I hear what they're

7   saying, but it's back to the question I was raising

8   this morning. We're buying into the idea that the

9   hazard ratio, the relative risk is our measure of

10   constancy. And are you saying that you have evidence

11   or that we have data because of the different drugs

12   that are being taken, the different patient

13   populations, that we are seeing different relative

14   risk at the end of the studies or just that the

15   patient populations are different? I'm not sure I

16   followed that you did all the analysis to show that

17   the relative risk are jumping all over the place

18   depending on the drugs that we're dealing with.

19   DR. HARRINGTON: So, Ralph, could you be a

20   bit more specific? So what they showed us is that the

21   point estimates, if I'm correct, go from .78 to .83 to

22   .93. And they make the case that that's the

1   observation over time and that you've noted two

2   variables that might have changed. The drugs are

3   clearly different. That's something that I'd like to

4   hear a little more about, and the populations as it

5   was described are a bit different. Is there something

6   --

7   DR. D'AGOSTINO: What I'm saying is these

8   numbers are jumping around, but are they sort of

9   significantly different? Are we really carrying a

10 message that the patient population has changed, the

11 drugs that people just bring into these studies now,

12 concomitant medication, is just so dramatically

13 different that the relative risk really has changed or

14 are we just seeing bouncing around with study by

15 study?

16   DR. HARRINGTON: Which is Dr. Yusuf's point

17 as he goes from 20 years of trials of .8 to .9. He

18 made the comment that we should be reassured that

19 they're on the same boundaries.

20   DR. D'AGOSTINO: Right.

21   DR. HARRINGTON: Bob?

22   DR. TEMPLE: That's a good question. There

1   was some discussion of this earlier. Our bias -- you

2   would never say this is proved. Our bias is that

3   hazard ratios could still be the same but risk

4   reduction could still be the same even if the

5   populations differed some in terms of risk or

6   conceivably even if you added another drug that

7   reduced the overall risk. They're all on aspirin now.

8   We're all on lipid-lowering drugs now. And so the

9   overall risk has decreased.

10   But the observation here is that the point

11 estimates have declined. That's apart from any

12 differences in population. That's apart from any

13 differences in what their underlying risk is. And

14 that's the question. Are we no longer really sure

15 that the risk reduction is as big as it was in HOPE?

16 I'm not trying to answer that, but I'm saying that is

17 --

18   DR. HARRINGTON: So let me ask you, Bob,

19 just because I had a bit of the same feeling that

20 Ralph did. But I'm troubled a little bit as well that

21 they're different drugs. I mean, if we had three

22 sequential trials with ramipril where the point

1   estimate went from .78 to .83 to .93, but that's not

2   what we have. We have three different chemical

3   entities.

4   DR. TEMPLE: This comes up all the time.

5   Sometimes people take all of the drugs within a class

6   and pool the results because it gives a narrower

7   confidence interval and a larger risk to rule out.

8   You get a bigger M1, so they do that.

9   It can also work the other way. If the

10   first study has the best result, then if you add the

11   others, it now gets smaller. There's no perfect

12   answer to this. But if you really believe that the

13   drugs are pharmacologically very, very similar, and

14   there's certainly a lot of underlying assumptions that

15   ACE inhibitors and ARBs are all pretty similar, and I

16   think that has a lot to do with why some people would

17   argue we should feel reassured about all this, then it

18   doesn't seem crazy to take a look at what -- well,

19   this comes up with 2b3a inhibitors all the time. I

20   mean, the results vary a lot. Do you just take the

21   one result that was best and use that as your active

22   control or do you try to look over the whole bunch of

1   data? There's no perfect answer.

2   It would be hard to argue that if you really

3   saw no result at all with a drug in the same class, it

4   would shake you a little bit on whether HOPE was good,

5   but those differences, as Ralph says, maybe they

6   aren't enough to shake you. That's sort of why we're

7   here.

8   DR. HARRINGTON: Ralph?

9   DR. A'GOSTINO: Do you have an answer?

10 Should we be shaking one of the speakers, not

11 necessarily you.

12   DR. TEMPLE: No, that's what we're asking.

13 I don't think you can ignore those other results.

14   Now, Salim said some things about what was

15 wrong with the PEACE study that we have not tried to

16 come to grips with, to my best knowledge. And maybe

17 that needs more attention because, as everybody's

18 pointed out, if you just pool the two of them, if you

19 just pool HOPE and EUROPA, it doesn't really matter

20 much because their combined results are very similar.

21   We go through this in our -- what should you

22 use? Should you use the worst result ever seen?

1   Should you average them? When you do average them,

2   what techniques should you use to average them? Those

3   are all unanswerable in some sense and, yet, you have

4   to come to grips with them.

5   DR. HARRINGTON: Yes, the question could

6   almost become, Bob, what's the outlier here. Is HOPE

7   the outlier or is PEACE outlier? And as you say, if

8   you make the assumption that PEACE is the outlier and

9   you just look at HOPE and EUROPA, I think the

10 statistical reviewer showed us that the margin

11 wouldn't change a whole lot.

12   DR. TEMPLE: It wouldn't change much, right.

13   DR. HARRINGTON: Sanjay and then Jonathan.

14   DR. KAUL: I guess the fundamental issues

15 I'm trying to come to grips with and I guess the FDA

16 is also grappling with it, otherwise I don't think

17 they would have assembled us to adjudicate on this

18 matter, is how to reconcile the paradox, which is

19 inherent in the database, the so-called continuum of

20 evidence. Assuming that the non-inferiority was met,

21 no matter what the choice of the non-inferiority

22 margin, the question is can a therapy be non-inferior

1 to a reference standard and yet not be superior to a

2 placebo at the same time. And that's the crux of the

3 matter in my head.

4   So what I would like the FDA to weigh in on,

5 is there a precedent for this and how have you

6 resolved that paradox in the past? And before you

7 answer, let me cite you an example, which I think

8 comes close but really doesn't answer it, is that of

9 the Valiant study.

10   Now, you can debate that the Valiant met

11 this pre-specified sponsor's criteria of non-

12 inferiority and would not have met an arguably more

13 robust non-inferiority margin of 1.09. But valsartan

14 was not, for want of a better word, handicapped by

15 subsequent placebo-controlled trials, which challenged

16 the efficacy of valsartan as is the case with

17 telmisartan.

18   So I would like some advice from the FDA how

19 to resolve this paradox, if it can be resolved.

20   DR. TEMPLE: Well, it isn't so much a

21 paradox as being sure that you know what you think you

22 know.

 1   There's no question you can show unequivocal

 2   non-inferiority measured statistically in a trial

 3   where the active control had no effect. Well, then

 4   that means absolutely nothing, and I have published

 5   examples of where that is. There are journals

 6   published trial after trial after trial comparing one

 7   drug with another drug, and they say okay, I see no

 8   difference; the other one works, but they hadn't made

 9   sure that the trial had what we call assay

10   sensitivity, which means that the control drug had an

11   effect of the defined size in that trial. That's why

12   the most important thing we think about all the time

13   is M1. Can we be sure of what the effect of the

14   control was in this study? That's the most important

15   single thing. Then you can ask how much of it you

16   should retain.

17   But you have to know that without measuring

18   it. And that's the problem with a non-inferiority

19   study. It always been the problem with a

20   non-inferiority study. So we agonize a lot, and

21   that's what you hear here, about how can we say what

22   the effect of ramipril was in this trial, not in HOPE

1   but in this trial. And you never can know if there's

2   no placebo. You can only make your best judgment, and

3   that's really what the discussion is about.

4   DR. HARRINGTON: Go ahead, Ralph. And then

5   I'll go to Jonathan.

6   DR. A'GOSTINO: This is part of the root of

7   my question about constantly saying about the

8   constancy being the relative risk. How do I know that

9   the drug, my active control, is working in these

10   things, no matter what the relative risk is? I mean,

11   we haven't addressed that at all here. It hasn't been

12   -- and I was going to raise it later on today.

13   But it's not just a matter of the relative

14   risk having some stability, but it's also a matter of

15   us believing that the active drug is showing itself in

16   this trial. And how do we address that with these

17   studies?

18   DR. TEMPLE: This is addressed in all of our

19   guidance. You have to --

20   DR. D'AGOSTINO: I know that.

21   DR. TEMPLE: You have to decide yes or no

22   that the past applies. And so you look at the design,

1   you look at the endpoints, you look at the patient

2   population, you look at the drop-out rates, you look

3   at all of those things.

4   As Salim said, poor quality will always make

5   things look the same. That's not a good incentive as

6   incentives go. But that's the judgment that we always

7   have to make as to whether these trials were similar

8   enough and whether there's reason to believe that the

9   active control had the anticipated effect, which is

10 how we determine M1, the margin that has to be ruled

11 out.

12   DR. HARRINGTON: We do have a bit of an

13 interesting perspective here, Bob, in that it's

14 unusual that you have the same study group having done

15 all of the studies. And so you have the McMaster

16 group having lead the HOPE trial, the McMaster group

17 having done these. I'm going to assume, but Professor

18 Yusuf can correct me if I'm wrong, that the endpoints

19 were defined the same way, that the ascertainment was

20 the same, that the adjudication was the same at least.

21 And to me, that's a measure of reassurance in some of

22 the issues that you brought up, that there is some

 1   constancy across the trials.

 2   Would you accept that?

 3   DR. TEMPLE: I think we would say that. The

 4   question is still has the world changed, has

 5   something, even if we don't know what it is, changed

 6   to make you doubt it. And the other two trials sort

 7   of go to that question. That's why we raise them.

 8   The process is you look at the historical

 9   experience and evaluate it as best you can and then

10   you make a very complex, very difficult, very hard to

11   define judgment about the likelihood that the effect

12   still applies, the constancy assumption. And you do

13   that every time you a non-inferiority trial. There's

14   no choice. You either don't do them anymore and say

15   one wins win or you make the best of it.

16   Bob was busy trying to --

17   DR. HARRINGTON: Go ahead, Bob.

18   Jonathan, I haven't forgotten you.

19   DR. O'NEILL: I probably can't add much to

20   this. But this conversation goes on in virtually

21   every medical drug area over and over and over again.

22   There's a discussion tomorrow for two days that

1 non-inferiority margin setting in for tuberculosis,

2 and it goes on in anti-infective.

3   Part of the value to the discussion today is

4 the logic of this. And getting back to what Ralph is

5 talking about, your only hope and it's not about HOPE,

6 but your -- I'm on target. Right.

7   [Laughter.]

8   DR. O'NEILL: The idea is that if you only

9 have a single study in the past of the active control,

10 you have no idea of whether if you were to run that

11 over and over and over again, you would repeatedly

12 demonstrate a difference. That's the rub.

13   So how do you back off and have a

14 conservative approach to that? Because, essentially,

15 you have no empirical evidence. And the reason why

16 you can't do non-inferiority trials in depression is

17 because there's a lot of evidence that even effective

18 anti-depressants in repeated placebo-controlled trials

19 cannot demonstrate differences.

20   So the issue here is in this non-inferiority

21 trial where telmisartan is compared to ramipril, where

22 it looks like they're pretty close together. You have

1   two alternative explanations. They're both

2   ineffective in this comparison or they're both

3   reasonably effective, but you don't know which is

4   which. And that is essentially, you need the fallback

5   position of what's called this historical evidence of

6   sensitivity to drug effect, meaning that in repeated

7   clinical trials, you'd be able to demonstrate that

8   ramipril always has an effect of delta, whatever that

9   might be.   So the issue here is, can you use

10   any of these other trials, other than HOPE, to give

11   you some of that comfort level. That's why some of

12   the other studies are being brought into the picture.

13   Can they bolster whether you repeatedly can show a

14   ramipril effect? And maybe even it's going to other

15   classes of drugs and whatnot, other drugs in the

16   class.

17   But the other issue here and I'm looking at

18   Dr. Zhang's slide on page 3, the fundamental

19   difference in choosing the lower bound of a confidence

20   interval for the historical data on HOPE is

21   essentially to protect you against the very thing that

22   we're talking about right now. That's why it's in

1 there. And it's not the discounting concept. It's

2 not a judgment of discounting for 50 percent. It's a

3 well recognized statistical principle of the

4 uncertainty, which is the 95 percent lower bound and

5 that's why that was chosen.

6   We aren't even at the discounting issue of

7 lack of constancy. If you want to have that

8 conversation, then you discount that lower bound

9 again. And then after you're there, then you have a

10 clinical conversation about how much of that do you

11 want to preserve. So you cannot confuse all these

12 issues.

13   And one of the issues that we're dealing

14 with in the non-inferiority guidance, which is about a

15 60-page draft, which will go out on the street

16 sometime probably in the next four months, three

17 months, two months --

18   DR. TEMPLE: Easy read, though.

19   DR. O'NEILL: It's an easy read. But it's

20 been trying to lay out the logic of these principles,

21 which are not easy for a lot of people to grasp. And

22 that's why I think this committee is being asked to

1 address many of these. And I think the way to deal

2 with it is to get in your mind what is the logic of

3 the layout of the problem.

4   DR. KAUL: I wanted to respond to

5 Dr. Temple's response to --

6   DR. HARRINGTON: You okay with that,

7 Jonathan?

8   DR. FOX: Yes.

9   DR. HARRINGTON: Okay. That's fine.

10   DR. KAUL: I think I wasn't quite sure what

11 your answer was, but I think Dr. Temple sort of

12 alluded to it. So let me just rephrase the question.

13   The assay sensitivity applies to historical

14 controls, but here we are sort of applying it to

15 future controls, aren't we? And so if I heard you

16 correctly, are you saying that because superiority has

17 not been established, we stop there? We don't go any

18 further? Please clarify.

19   DR. TEMPLE: I'm not sure I understand, but

20 let me -- as Bob said, he used the term historical

21 evidence of sensitivity drug effects. We abbreviate

22 that HESD in the ICH E-10 document. That tells you

1   what the drug did in the past. You then are obliged

2   to bring to the present what you know about that and

3   what you know about the present study to reach a

4   conclusion of whether it's likely, because you're not

5   measuring it, that the control drug had a similar

6   effect in the new study. And if you are prepared to

7   say it did, then you would say the trial has assay

8   sensitivity. That is, it could have

9   distinguished -- because it had the drug that had an

10 effect, it could have distinguished the drug that did

11 have an effect from a drug that didn't.

12   But of course, the determination of assay

13 sensitivity is a judgment. It's not proved. You

14 don't have a placebo in the new trial. And any

15 non-inferiority study has this problem. You have to

16 make a judgment based on the best data you can.

17   So that's why we worry about was the effect

18 variable in the past. You don't want to pick just the

19 best study. You want to see what the result's at

20 because that's going to help you determine whether you

21 can reasonably conclude that the new trial has assay

22 sensitivity. You will also look at the quality of the

1   trial. If everybody dropped out, that's going to give

2   you a bias towards the null; that would be bad. So

3   you look at all those things.

4   But in the end, it's still a judgment, which

5   is obviously distressing. It's not like p less than

6   .05.

7   DR. KAUL: I don't want to put words in your

8   mouth, but if that has not been established, you stop

9   there. Don't proceed further. Is that your position?

10   DR. TEMPLE: If what is not? If you can't

11   conclude that ramipril had an effect in the new trial,

12   then we would say don't even start the study. Thanks.

13   DR. HARRINGTON: Bob, I want to go back to

14   something that you were just making your point. And

15   when the ONTARGET investigators planned their study,

16   the only knowledge that was available to them was

17   ramipril. And they didn't have EUROPA and PEACE.

18   They were ongoing, but they didn't have that data.

19   Help us understand as people are planning

20   trials the best evidence available at that time was

21   HOPE, they chose that then as their comparison to see

22   if they could make a step forward, have an alternative

1 approach to ramipril.

2   Is this approach just flawed when new data

3 might enter the arena over the years? Does one have

4 an opportunity to adapt as things are going on or is

5 the point of taking a more conservative boundary in

6 part trying to guard against that?

7   DR. TEMPLE: You didn't say which Bob.

8   DR. HARRINGTON: I'm sorry. Bob O'Neill.

9   DR. O'NEILL: Well, the problem with the

10 non-inferiority trial is that you have further

11 discounting to your non-inferiority margin even after

12 the study is done if the study that you've done

13 differs significantly from the studies that were done

14 in the past. And you never know that until you're

15 done.

16   So that's the whole problem or like Salim

17 says, that's what makes non-inferiority trials so

18 difficult, also, because the conduct of the trial as

19 well as if you couldn't control, let's say, some

20 things that were controlled similarly in past studies,

21 you have to in some sense pay some price for that,

22 whether it's through a discounting or adjusting for

1   the covariates in your current study relative to the

2   covariates in the past study, particularly under a

3   situation where you might have what we call effect

4   modification or treatment by subgroup interactions.

5   So the idea here is you may have to -- you

6   can only do what you did on the basis of a single

7   study. But I think even another question, and it's

8   very difficult in these large trials where you have

9   composite endpoints -- the choice of whether you took

10   a 3-composite or a 4-composite is very critical to a

11   non-inferiority trial because one way of making a

12   non-inferiority trial successful when it should not be

13   is by throwing in neutral events because neutrality

14   works in your favor --

15   DR. HARRINGTON: It diminishes the overall.

16   DR. O'NEILL: -- and it diminishes the

17   effect size. So essentially, if you deconstruct these

18   and all you knew back then was the 4-component versus

19   the   3-component but then you had to take your

20   chances on what was the appropriate endpoint for

21   ONTARGET. And it turns out that that's an interesting

22   conversation in its own right as to whether three

1   components or four components because even the studies

2   that fail or don't fail, they fail or don't fail on

3   the basis of whether they're a 3-component or a 4-

4   component. And there is value to understanding the

5   placebo-control comparisons as to which of those

6   endpoints in the composite is causing the trial to

7   fail, because if you take that idea and you look at it

8   in a non-inferiority trial, you're sort of saying this

9   is contributing to non-inferiority when it should not,

10   which is another thing that they probably wouldn't

11   have known because all they had was HOPE at that time.

12   DR. HARRINGTON: So you don't have a full

13   understanding of which events are actually modifiable

14   along the way.

15   DR. O'NEILL: Right, right.

16   DR. HARRINGTON: Go ahead, Bob, and then I

17   will get to you, Jonathan.

18   DR. TEMPLE: Well, you asked specifically

19   what happens if new trials come out that might cause

20   you to readjust it. And although we generally say you

21   go with what you started with, we would certainly look

22   at additional trials that shed new light on what the

1 hazard ratio was for the drug. You can't not do that.

2 They had no choice but to use HOPE, but you got to at

3 least consider what the implication of subsequent

4 trials are.

5   I do want to remind everybody of Dr. Zhang's

6 Slide 26, which goes to one of the points that Bob

7 raised, that we are saying that when you do the -- if

8 the old trial when analyzed -- like if you analyzed

9 HOPE and found that there were major differences,

10 depending on whether you were on this drug or that

11 drug or this drug or that drug, we would look at the

12 new trial and see if there were major differences on

13 some of those things that appeared to have a major

14 influence. And it's hard to plan that, but that's one

15 of the things that we would certainly incorporate to

16 the analysis.

17   So your estimate of what M1 is might change

18 if the populations were very different. Now, I found

19 her Slide 26 moderately reassuring, not too many

20 things seemed to influence the result.

21   DR. HARRINGTON: Although there is a pretty

22 important one here, the anti-platelet therapy, which

 1   really changed in its usage, right?

 2   DR. TEMPLE: Right, except for platelets.

 3   Yes, but the use was low in all groups.

 4   DR. HARRINGTON: Go ahead, Jonathan.

 5   DR. FOX: I just want to maybe introduce a

 6   slightly different topic. I think the statistical

 7   discussion has been quite detailed. We're going to

 8   have more debate this afternoon about non-inferiority

 9   and all that stuff. And I suspect that in the end

10   this panel may well come down to, as Professor Yusuf

11   suggested, taking into consideration all the data and

12   looking at the best estimate of clinical benefit that

13   might accrue to this product in this patient setting.

14   In that context, I'd kind of like to pose

15   maybe a question to Dr. Temple or other members of the

16   agency in terms of the criticism that I think I heard

17   leveled against Dr. U's contention that this was T

18   versus placebo on a background of.

19   Now, in other areas of drug development like

20   a combination anti-hypertensive therapy, combination

21   oral anti-diabetic therapy, typically trials are run,

22   new agency versus placebo against a background of

1   metformin against a background of hydrochlorothiazide,

2   what have you. And I remember a meeting some years

3   back that I participated in with Dr. Temple where in

4   the context of combination anti-hypertensive therapy,

5   he very clearly told us well, two drugs are better

6   than one, why should that be a surprise? And in that

7   context, it was pretty obvious, anyway.

8   I guess what I'm trying to get at is in this

9   context, one of the questions posed by the trial was

10 dual renin-angiotensin blockade versus single

11 renin-angiotensin blockade. As Dr. Temple said, the

12 two classes of renin-angiotensin agents, ARBs versus

13 ACE inhibitors, are pharmacologically similar but

14 maybe not identical. Maybe it was a fair scientific

15 question to ask is two better than one.

16   But if everybody thought they already knew

17 that they're pharmacologically or medically

18 equivalent, then why bother doing any of these trials?

19 And if you think that they're pharmacologically

20 distinct enough, to perhaps have accrued benefit from

21 the combination, then I think Dr. U's contention that

22 this is new versus placebo on a background of other is

1   at least worth consideration.

2   So I don't know if you have comments about

3   that, Dr. Temple.

4   DR. TEMPLE: The only point is there are two

5   different questions. Whether an ARB adds to an ACE

6   inhibitor is a perfectly good question that's being

7   asked in multiple settings, and sometimes it seems to

8   add and sometimes it doesn't.

9   That's not the same question as whether an

10 ARB is better than placebo. So the two trials that

11 were against placebo seem highly relevant to the

12 non-inferiority question --

13   DR. FOX: Totally agree.

14   DR. TEMPLE: -- because the non-inferiority

15 question is trying to answer that same question,

16 although in an indirect way without a direct

17 comparison.

18   I just didn't think that whether ARBs add to

19 ACE inhibitors had much to do with whether ARBs are

20 better than placebo. So I think there are two studies

21 that are highly relevant because they leaned, but they

22 didn't win. That seems highly relevant to the

1   interpretation of the non-inferiority study. The fact

2   that ARBs don't add to ACE inhibitors does not seem

3   relevant to the question of whether ARBs are better

4   than placebo.

5   DR. FOX: I'm actually asking you a more

6   general question for us drug developers, in general,

7   who are looking to introduce new therapies in

8   different therapy areas. And when is the pharmacology

9   of a new class of agent either different enough or too

10 similar to design the trial that way?

11   DR. TEMPLE: That's what you have to figure

12 out. I don't know.

13   DR. FOX: I'm looking for your advice.

14   DR. TEMPLE: Well, my betting would have

15 been that it's very unlikely that an ARB's going to

16 add to an ACE, and, yet, there are now studies out

17 where it's asserted that they do, somewhat to my

18 surprise. We never know what we think we know. So I

19 think it's always worth looking.

20   DR. FOX: Advice taken.

21   DR. HARRINGTON: Let's go to Dr.

22 Stockbridge, then Emil, then David.

1   DR. STOCKBRIDGE: I just wanted to point out

2   that half the money was spent testing whether or not

3   the combination was going to be superior to ramipril

4   alone. And had that been positive, it would certainly

5   have contributed to the understanding of whether or

6   not it was effective against placebo.

7   DR. HARRINGTON: So let me finish the

8   sentence for you. That means that we should at least

9   consider the information offered by that arm of the

10   study as we have this continued discussion.

11   DR. STOCKBRIDGE: Well, I think you can't

12   dismiss the implications for a false positive finding

13   from the rest of the trial based on what you think you

14   now understand about the relationship between ACEs and

15   ARBs.

16   DR. HARRINGTON: So, Ralph, you first

17   brought it up, you want to comment?

18   DR. D'AGOSTINO: I just wanted to clarify a

19   couple of things I said. I'm concerned about ignoring

20   the combination versus the single ingredient. And I

21   raised that this morning, the question that that's

22   part of the totality of information. So I think we

1 need it. So that was one comment that I made and I

2 very much stay with that.

3   The second comment was it's not a

4 placebo-controlled trial, the combination. And I

5 think that's been clarified. So it doesn't give us

6 information about this drug versus placebo. But it

7 does absolutely give us information, which I think we

8 need in the totality, if we use that word once again.

9   DR. HARRINGTON: Go ahead, Emil, then David.

10 And then I think we'll break for lunch.

11   DR. PAGANINI: The whole idea of going

12 through non-inferiority has always been difficult. As

13 I see it, there are three types of drugs that come on.

14 There's either new drug Allol (ph), which is a new

15 admission. There's a better drug, Alil (ph), which is

16 a superior drug to whatever. And then there's a

17 similar drug, Aprine (ph), which is basically looking

18 at I'm the same drug as something else and so

19 therefore, I'm not inferior.

20   When you then bring those three up, they

21 have three different ways of looking at it. Since our

22 role is supposed to be efficacy and safety, efficacy

1   is important but across a background of safety. And

2   so if the drug is safer, maybe your NI may be a little

3   bit less stringent because you say well, I'll trade

4   off safety for efficacy to a certain extent.

5   However, when you look at a safety induced

6   placebo-controlled where the population, for example,

7   in TRANSCEND was supposedly being those that were

8   resistant or intolerant of ACE inhibition, yet the

9   population had them and others, as I understand -- it

10 wasn't just the resistant. So I'll ask industry to

11 follow up. I think that population was a mixed

12 population, not just resistant. And you found no

13 effect against placebo. And that sort of makes me a

14 little bit less happy about the safety issue and about

15 the effectiveness.

16   Then finally, when you're using a target

17 drug against which you want to be non-inferior and

18 that target moves, as we saw yesterday and we've seen

19 in a lot of times, that target moving, moving target,

20 makes any study very difficult to interpret and very

21 difficult to come up with a specific answer.

22   So what I'm hearing is that the moving

1 target is a very difficult thing for industry but it's

2 even more difficult for FDA as time moves on and

3 populations change.

4   So I don't know the answer to that, but

5 that's what we're stuck with. And the basic question

6 to industry, TRANSCEND, only ACE intolerant or was it

7 a whole group, and then in the second, what was the

8 reason for submission? Was the reason for submission

9 to have the same drug? Is that for a drug labeling

10 issue or was it adding something to the treatment of

11 patients? If it was a safety effect, I'd say it was

12 adding something. But it didn't see that. So now I

13 go back to why are they doing that.

14   DR. HARRINGTON: Go ahead, Bob. And then

15 I'll let Dr. Yusuf talk about TRANSCEND.

16   DR. TEMPLE: And they'll have to tell you

17 why. It does seem obvious they were hoping to find an

18 additive effect. They, as Norm said, devoted a lot of

19 effort, money and time to doing that. But they were

20 unable to show that. That would have been a major

21 advance, obviously.

22   They also pointed out that not everybody can

 1   tolerate an ACE inhibitor. So I just want to once

 2   again make the distinction between M1 and M2. You

 3   can't give much on the question of whether there's any

 4   effect at all. So M1, you have to be really very

 5   sure. As Bob explained, that's why we take the lower

 6   bound for the confidence interval to determine and all

 7   that stuff. You want to be quite sure.

 8   M2 is a little more flexible, and it could

 9   depend on how you're going to use the drug. This

10   hasn't come up, but one could think of this as a drug

11   for people who can't tolerate ACE inhibitors. Now, in

12   that event, you might now be so insistent on meeting

13   M2 as long as you thought that it had some effect that

14   you couldn't get any other way.

15   So the how much to preserve and how good the

16   evidence has to be has somewhat more flexibility in

17   it. That's what our document's going to say. You got

18   to sort of think about that as long as you're totally

19   sure it has some effect, well, pretty sure.

20   DR. HARRINGTON: Dr. Yusuf, would you

21   comment to answer Dr. Paganini's question on the

22   patients that made up TRANSCEND? And then I'll ask

 1 David to ask his question.

 2   DR. YUSUF: That wasn't why I stood up, but

 3 I'll make that comment. The patients who made up

 4 TRANSCEND were largely people who were documented to

 5 be intolerant to ACE. And the majority of it, 90

 6 percent, there was documentation they had cough. And

 7 that was the reason. About 5 percent was because of

 8 hypotension and about 1 percent renal dysfunction.

 9 Eight percent were other reasons out of which the

10 commonest was angioedema, previous angioedema, and a

11 smaller proportion was rash. So some of these are

12 more serious like angioedema. Some of them are

13 nuisance like cough, and some of them are vague like

14 rash. But these are documented. We had to document

15 it.

16   The point I was trying to raise, if I may --

17   DR. HARRINGTON: If it's brief or otherwise,

18 we can do it right after lunch.

19   DR. YUSUF: I'll try to make it brief

20 because I'd like you to hear it before lunch. I'm

21 happy to elaborate later, two, three things. The most

22 important thing is the point that Sanjay Kaul raised,

1   do we have any evidence that there is sensitivity in

2   the superiority trials. And in considering that, I

3   want you to think of three things. One is they're not

4   the same population, ACE intolerance, not the same.

5   Second, the post-stroke thing is not the same. The

6   third is I agree with the FDA reviewers. If you use a

7   line and the primary endpoint, you'd write fail, fail,

8   fail. But if you look at the entire scorecard, which

9   is all the exams that are possible, everything that

10 happened, that is all the events and the

11 consistency -- and this is the slide, if you can show

12 it -- then you'd say well, there's something

13 happening.

14   I want to go down to the TRANSCEND thing,

15 and you will see it suggests on the triple endpoint.

16 And I agree with the FDA reviewers. If you adjusted

17 the p-value, it will become 058, so that's fine. But

18 I think all of us, the FDA's not only a kinder,

19 gentler, but they're a more sensible organization than

20 many of us are. And they will agree 058 is not

21 different from 059. We're not p-value specialists;

22 we're trying to --

1   So TRANSCEND on that endpoint is not clear,

2   suggestive. But then you look at multiple endpoints

3   on the original quadruple. There is actually a more

4   marked difference than looking at first endpoint. And

5   I hope some of the discussion will be at looking at

6   the totality of the burden. You look at

7   cardiovascular hospitalizations. Again, it's

8   consistent.

9   So looking at TRANSCEND overall, you're

10   feeling there is an effect. I'm not saying it's the

11   same as in HOPE. I'm just saying there is a

12   clinically important benefit. And you see that again

13   when you do the meta-analysis in different ways.

14   So to address a key issue is in the modern

15   context, is there some evidence that telmisartan is

16   doing something? Ethically, we can't do it in

17   identical population. But in a first cousin

18   population, I'd like to say, yes, there is. It may

19   not be the same as we'd have hoped from HOPE, but

20   certainly, there's something there, and you've got to

21   decide whether that is clinically relevant.

22   DR. HARRINGTON: I appreciate you putting

 1 this up. You're getting at the essence of what we'll

 2 do this afternoon in terms of thinking of all the

 3 data.

 4   David, you have the last question before

 5 lunch.

 6   DR. DeMETS: I just want to follow up on a

 7 technical question. On Slide 8 from the FDA's

 8 presentation, there's a passing footnote about not

 9 adjusted for multiple comparisons. I'm wondering what

10 multiple comparisons you had in mind, which may take a

11 comment. And as the second part of that question,

12 Ralph D'Agostino this morning asked about adjustment

13 of alpha. We really have two. There's many multiple

14 comparisons going on here, but at least one

15 comparison. I mean you have two comparisons. You have

16 the combination versus ramipril and you've got the

17 non-inferiority part. So are we doing any -- and in

18 the document the FDA reviewers put together, there was

19 some comment about what should the alpha be when you

20 have two comparisons. And no one's brought that up

21 today except as a reference to multiple comparisons.

22   So I'm just trying to clarify in my mind

1   what adjustment you're thinking about and what was

2   also your alpha position on the fact that there was

3   actually two legitimate comparisons in the ONTARGET

4   study. I'm not talking about adjusting for two

5   endpoints. I'm just talking about two comparisons.

6   DR. HARRINGTON: Are you talking about

7   splitting alpha for the two comparisons?

8   DR. DeMETS: Well, that's what I want to

9   what the opinion is.

10   DR. HARRINGTON: Dr. Zhang?

11   DR. ZHANG: This p-value is not adjusted for

12   multiple comparison because they showed a 95 percent

13   confidence interval. As I mentioned, for the

14   non-inferiority trial, they have --

15   DR. DeMETS: No, but what multiple

16   comparisons are you alluding to here? I have no idea.

17   There's lots of them.

18   Which ones are you thinking about?

19   DR. ZHANG: Oh, okay. The TRANSCEND --

20   DR. DeMETS: Slide 8.

21   What multiple comparison are you referring

22   to? I have no idea.

1   DR. ZHANG: The thinking -- well, it's not

2   exactly the precise term for adjustment for multiple

3   comparison. The thinking first is you look at the

4   primary endpoint. It failed. Then should you look at

5   the secondary endpoint at all?

6   DR. DeMETS: Okay. That's what you're

7   getting at.

8   DR. ZHANG: Then if you present the

9   4-component endpoint and 3-component endpoint at the

10   same time, you sort of looking at them at the parallel

11   way and so that's why we referred to --

12   DR. DeMETS: Okay.

13   DR. HARRINGTON: So you're really talking

14   about a hierarchical testing strategy where you failed

15   on the first and then you stopped.

16   DR. ZHANG: That's right.

17   DR. HARRINGTON: Okay.

18   DR. DeMETS: So then the second point of my

19   question --

20   DR. TEMPLE: No, she's considering it both

21   ways. She's saying you can think of it that way in

22   which case you can't go on to the three. She's also

1 saying suppose you thought they were co-primary

2 endpoints; what kind of adjustment would you make?

3   DR. HARRINGTON: In which case you might

4 have to have the alpha distributed some way.

5   DR. TEMPLE: Some adjustment except there's

6 overlap on three of the components.

7   DR. DeMETS: So then the other question is

8 to get an answer to what Ralph asked is there's two

9 comparisons, the combination versus --

10   DR. ZHANG: For ONTARGET.

11   DR. DeMETS: For ONTARGET, yes. You made a

12 comment to it in your document, but you haven't

13 resolved that in my mind for today. And I think Ralph

14 was asking about that, and I don't think we got an

15 answer.

16   DR. ZHANG: So could you clarify your

17 question?

18   DR. DeMETS: Yes. You have a combination

19 versus ramipril. That's one. That was the

20 superiority part. You have a second study, which is

21 the non-inferiority study. So normally, if you said

22 you had two comparisons in the study, you would divide

1   alpha by two or something.

2   DR. ZHANG: That's correct.

3   DR. DeMETS: Well, they didn't do that, and

4   you alluded to it in your review, but we haven't sort

5   of settled it here.

6   DR. ZHANG: We did that because I commented

7   that the 97.5 confidence interval the sponsor showed

8   is a two-sided interval for the non-inferiority test.

9   So it's already taking a --

10   DR. DeMETS: .05 one-sided is equal to .05.

11   DR. D'AGOSTINO: One of the questions I was

12   raising was there implicit hierarchy in what you were

13   looking at. I mean you can after the fact divide by

14   two. But what were they thinking about? And that's

15   really part of what I was asking.

16   DR. TEMPLE: Well, they clearly had both

17   endpoints in mind. The question is whether looking at

18   a wider confidence interval for non-inferiority

19   accounts for that.

20   DR. HARRINGTON: If you could keep it brief,

21   otherwise we'll follow up after lunch. Go ahead.

22   DR. SCHUMACHER: I'm Helmut Schumacher. I

1 was the statistician from BI. And we had used the

2 Hochberg procedure to adjust for the two primary

3 hypothesis. In case both p-values, one-sided p-values

4 had been below 2.5 percent, everything would have been

5 okay. Because the combination hypothesis, we had to

6 adjust the comparison, the non-inferiority comparison,

7 and that's why the p-value, the one-sided p-value of

8 1.25 percent was relevant. And the 97.5 two-sided

9 confidence intervals are given in all our tables.

10   DR. HARRINGTON: Does that satisfy you,

11 David?

12   Ralph, are you okay with that answer?

13   DR. D'AGOSTINO: Yes, I believe that's what

14 was said this morning to me. My reading is I couldn't

15 find that clearly stated, and I appreciate the

16 reiteration of it.

17   DR. HARRINGTON: Okay. So we're doing

18 pretty good on time here. It's a little after 12:10.

19 So why don't we say we'll be back around 1:10, and

20 we'll start with the open public hearing.

21   (Whereupon, a lunch recess was taken from

22 12:11 p.m. to 1:16 p.m.)

1   A F T E R N O O N   S E S S I O N

2   DR. HARRINGTON: If I could have people take

3   their seats, we'll go ahead and get started. We're

4   now going to open up the open public hearing session

5   portion of these meetings. And I'm required to read

6   the following statement.

7   Both the FDA and the public believe in a

8   transparent process for information gathering and

9   decision making. To ensure that such transparency at

10   the open public hearing session of the advisory

11   committee meeting, the FDA believes it is important to

12   understand the context of an individual's

13   presentation. For this reason, the FDA encourages you,

14   the open public hearing speaker, at the beginning of

15   your written oral statement to advise the committee of

16   any financial relationship you may have with the

17   sponsor, its products and, if known, its direct

18   competitors.

19   For example, this financial information may

20   include the sponsor's payment of your travel, lodging

21   or other expenses with your attendance at this

22   meeting. Likewise, FDA encourages you at the beginning

1   of your statement to advise the committee if you do

2   not have any such financial relationships. If you

3   choose not to address this issue of financial

4   relationships at the beginning of your statement, it

5   will not preclude you from speaking.

6   The FDA and this committee place great

7   importance on the open public hearing process. The

8   insights and comments provided can help the agency and

9   this committee in the consideration of issues before

10 us. That said, in many instances and for many topics,

11 there will be a variety of opinions. One of our goals

12 today is for this open public hearing to be conducted

13 in a fair and open way where every participant is

14 listened to carefully and treated with dignity,

15 courtesy and respect. Therefore, please speak only

16 when recognized by either myself and Elaine, and thank

17 you for your cooperation.

18   So I believe we have one registered open

19 public hearing speaker. It is Mr. James Baranski from

20 the National Stroke Association. Mr. Baranski.

21   MR. BARANSKI: Thank you, Mr. Chairman,

22 members of the committee. Thank you for your time and

1 attention. A note of disclosure, the sponsor did not

2 pay for my travel to be here. The sponsor has

3 provided support to National Stroke Association in the

4 past as has its competitors.

5   I'll keep my statement brief. I expect that

6 your discussion this afternoon will be robust and

7 lively and hopefully on target and transcend to great

8 hope. I couldn't help that.

9   Who said the researchers didn't have a sense

10 of humor?

11   I'd like to share with you today actually an

12 article I read yesterday in the Wall Street Journal.

13 And I appreciate that the Wall Street Journal

14 isn't -- or I don't expect that it's recognized by the

15 National Libraries of Medicine. But nonetheless, it

16 was an article that the headline was Healthcare Isn't

17 a One Size Fits All. And the genesis of the article

18 was really to explore all of the issues surrounding

19 the great debate in healthcare reform. And the notion

20 of quality service, quality treatments compared to

21 quantity of services and treatments was explored. And

22 apparently, it's one of the latest issues that health

1 reform is considering in an attempt to balance the

2 cost of whatever healthcare may look like in the

3 future, so this whole issue of quality versus

4 quantity.

5   As I read the article, it struck me

6 that -- and particularly as I listened to the

7 discussions this morning, this whole issue concerning

8 quality and the need and the importance of balancing

9 quality with safety and in this situation, for

10 example, with ACE intolerance. And in my world, the

11 world of stroke, that's a significant issue,

12 recognizing that there's some 6.4 million stroke

13 survivors in this country. It's projected that there

14 will be 780,000 new strokes this year. So it's a huge

15 issue.

16   As many of you know, many of you clinicians

17 know, there aren't a whole lot of tools in the toolbox

18 in terms of preventing stroke and in terms of treating

19 stroke. In fact, it wasn't until 1996 that the first

20 indication for the treatment of stroke came online.

21 So in the timeline of stroke, that's pretty

22 incredible, considering Hippocrates writes of stroke.

 1   So anyway, back to the article. So again,

 2   as I'm reading it, I'm struck by this whole issue of

 3   quality, quantity and I'm equating that to stroke and

 4   the lack of quantity of services available. And I

 5   have to say how impressed I am of the committee's

 6   concern over efficacy as it relates to quality in this

 7   topic. But again, I'd like to make certain that we

 8   recognize that this may be an opportunity for us to

 9   add to the quantity of those treatments available for

10   the prevention of stroke, particularly considering the

11   balance, that delicate balance between safety and

12   efficacy.

13   I thank you all for your time. I thank you

14   for your attention.

15   DR. HARRINGTON: Thank you, Mr. Baranski.

16   If there are no further registered speakers,

17   it's then asked of me to read the following:

18   The open public hearing portion of this

19   meeting is now concluded, and we will no longer take

20   comments from the audience. The committee will now

21   turn its attention to address the task at hand, which

22   is the careful consideration of the data before the

1   committee as well as the public comments previously

2   made.

3   So in terms of the timekeeping, we have the

4   rest of the afternoon devoted to really two tasks.

5   One is to finish up the questions that panel members

6   might have of either the sponsor or the FDA. And I'd

7   like that to be as exhaustive as it needs to be. If

8   you felt that things are answered, we could certainly

9   move on. But if you have additional questions, now's

10 the time to ask it because when the questioning comes

11 to an end, I'd then like to turn our attention to the

12 series of questions.

13   You'll note that FDA's provided us with a

14 series of questions, I think it's six, which

15 culminates in a voting question at the end. So the

16 first five are really issues for us to discuss and try

17 to bring our attention to certain items that Dr.

18 Stockbridge and others are looking for our advice on.

19   So I'll open up to the panel to be able to

20 particularly ask the sponsor if there are any

21 additional questions that remain or the FDA.

22   Emil?

1   DR. PAGANINI: To the sponsor, one of the

2   added, the fourth element was the CHF hospitalization.

3   Was there a strict admission criteria for that or was

4   that left up to the investigator?

5   DR. YOUNG: Since I participated in a lot of

6   the definitions on trial design and am a heart failure

7   cardiologist as well, this is a very important issue

8   and a very important question to us. And if you look

9   at the definition of hospitalization for congestive

10   heart failure, first, there are two important

11   components of that, number one, hospitalization and,

12   number two, the diagnosis of congestive heart failure.

13   And if you looked at how that was determined in the

14   trials of both ONTARGET and TRANSCEND, newly diagnosed

15   congestive heart failure was defined as symptoms and

16   signs typical of heart failure, so orthopnea, jugular

17   venous depression, peripheral edema and radiologic

18   evidence of CHF.

19   The issue of hospitalization then comes up

20   and is variable. There was not a surrogate for

21   hospitalization. This was not ED visits. This was

22   not urgent clinical visits. And there was an

 1   amendment that developed during the progress of the

 2   clinical trial where hospitalization for CHF was

 3   defined originally as for CHF or attendance in an

 4   acute care setting to CHF and attendance in a specific

 5   emergency room for treatment of that congestive

 6   episode.

 7   Now, one has to remember that this was an

 8   international trial. And so there is variability in

 9   heart failure hospitalizations from North America

10   throughout Europe and other areas where this was

11   present.

12   So that was specifically how heart failure

13   was defined and obviously is important as that was the

14   fourth endpoint in the 4-part endpoint that was

15   chosen.

16   I don't know if that answers specifically

17   your question.

18   DR. PAGANINI: Well, it's the one that falls

19   out. And the three when you look at the three,

20   everything is fine. The one that falls out is very

21   variable and may be very subjective and that's one of

22   the issues that we sort of have to deal with.

1   While I have the mic, can I ask one other

2   question?

3   DR. HARRINGTON: Absolutely.

4   DR. PAGANINI: In the covariate analysis,

5   why wasn't renal function used? Did it not come out

6   as a variable for outcome?

7   DR. HARRINGTON: Who's the question to?

8   DR. PAGANINI: To either --

9   DR. HARRINGTON: Is it the FDA analysis that

10 we saw?

11   DR. PAGANINI: Yes.

12   DR. HARRINGTON: If the FDA reviewers could

13 comment, I think it's when they looked at the various

14 subgroups.

15   DR. PAGANINI: Correct. Defined by any way

16 you want to define it, anything from a serum

17 creatinine greater than 1.2 or 1.4 to chronic kidney

18 disease to anything like that. Did it fall out?

19 Because it usually is a fairly robust factor in

20 outcome studies, virtually across the board.

21   DR. HARRINGTON: So we've got an answer on

22 both sides. So while the FDA reviewer is looking, it

1   looks like Dr. Yusuf might have an answer from his

2   perspective.

3   So, Salim.

4   DR. YUSUF: Yes, we did look at it because

5   it was something we were interested in. There was no

6   heterogeneity of effects either in ONTARGET or in

7   TRANSCEND. We haven't done a covariate adjusted, but

8   we've done a subgroup analysis. And that almost will

9   tell you there won't be a change when you do a

10   covariate analysis. I mean people with higher

11   creatinines are at higher risk because we were

12   interested in the effects on renal function as well,

13   so we did look at that. And I think there are two

14   papers that have come out, one in The Lancet and one

15   in Annals; Hansmann is the first author relating to

16   these.

17   DR. HARRINGTON: Does the FDA have more to

18   add to this? Yes.

19   DR. U: Can I get Slide No. 44? We did look

20   at the renal endpoint but didn't mention it because

21   the protocol specifies that this renal endpoint will

22   not be evaluated if either the non-inferiority

1 analysis or the superior analysis in ONTARGET fails.

2 And both failed, so we didn't present it this morning.

3 But we have it in our review.

4   It shows there was some report. The

5 ONTARGET trials shows that neither the telmisartan

6 plus ramipril combination nor telmisartan has any

7 advantage over ramipril for the primary renal

8 endpoint, which is in a population of patients who are

9 defined to have some diabetic nephropathy. No

10 advantage in deaths, although the combination seems to

11 have fewer percentage in terms of death. But there

12 are also more people who have a doubling of serum

13 creatinine in the combination group compared to the

14 telmisartan or ramipril alone.

15   So there is no signal in any way that the

16 drug or the combination has a benefit over the current

17 ramipril for the total composite of three endpoints,

18 three renal endpoints or each of the endpoints that we

19 looked at.

20   DR. HARRINGTON: Are you satisfied with

21 that, Emil?

22   DR. PAGANINI: (Affirmative nod.)

 1   DR. HARRINGTON: Are there other questions?

 2   Dr. Yusuf, this morning I made a comment

 3   that it was helpful to me to see that your group had

 4   actually coordinated all of the trials because at

 5   least I assumed, therefore, there was a consistency in

 6   the definition of the endpoints, the ascertainment of

 7   the endpoints, et cetera. But I assumed that.

 8   Can you tell me what the actual process was?

 9   Were the endpoints, particularly myocardial

10   infarction, cardiovascular death, stroke, similar

11   definitions and was the ascertainment the same?

12   DR. YUSUF: I think you're right. We ran

13   HOPE, ONTARGET and TRANSCEND but not PRoFESS, although

14   I was one of the members of the operations committee

15   of PRoFESS. In the first three trials, HOPE, ONTARGET

16   and TRANSCEND, the definitions of CV death, MI and

17   stroke were identical. The forms were essentially the

18   same. I mean there may have been some minor

19   differences. The chair of the adjudication committee

20   was the same person.

21   The degree of care we took in running all

22   three trials was identical. If anything, it was

1   better in ONTARGET and TRANSCEND because we just got

2   smarter over time and more experienced. Things like

3   lost follow-up was less, compliance was better in

4   ONTARGET. So the things that Bob O'Neill indicated

5   that you'd worry that the quality was any worse, in

6   fact, was the reverse. The quality of ONTARGET and

7   TRANSCEND in terms of completeness of follow-up,

8   accuracy of data, management, the accuracy, the

9   compliance, percent achieving full dose of ramipril

10 was higher in ONTARGET than in HOPE. So you're

11 absolutely right, Bob, it was.

12   I can't say that -- I mean, obviously, we

13 didn't run the PRoFESS study, but that too was run

14 very, very professionally.

15   DR. HARRINGTON: As best you know, the

16 definitions were the same?

17   DR. YUSUF: Were the same. Heart failure

18 had a slight difference, which I think Jim explained.

19 Having said that, in HOPE, the effects on heart

20 failure was consistent irrespective of the types of

21 definition. We looked at the types of investigated,

22 reported heart failure without verification, there was

1   a benefit. Adjudicated, there was a benefit.

2   Hospitalization, there was a benefit. And within

3   ONTARGET and TRANSCEND, based on whether you take --

4   actually, if you take investigator reported, the

5   results get better than what it is.

6   The other thing to point out is while I'm

7   here is that when you look at multiple events, heart

8   failure starts to go in the direction one would have

9   all hoped for. And that then -- because I was worried

10 when I saw the lack of effect, especially in TRANSCEND

11 on heart failure, that there may be something that's

12 counteracting the potential benefit. But when I saw

13 that examining multiple heart failure hospitalization,

14 it starts to trend the right way. So if you look at

15 repeat hospitalization, there's actually a 50 percent

16 lowering. So that's telling you we just had a bad

17 break on it. That's the way I read it.

18   DR. HARRINGTON: And since you brought it

19 up, with the multiple events, a question I had from

20 this morning, was the same rigor applied to all

21 events?

22   DR. YUSUF: Yes.

1   DR. HARRINGTON: Because frequently, as you

2   know, the first event and then the subsequent ones are

3   not --

4   DR. YUSUF: I think there are two things we

5   do in all our trials, and we did that in ONTARGET and

6   TRANSCEND that you wanted. First, we encourage people

7   to stay on the allocated therapy even after the first

8   event. So the only event where we did not encourage

9   them to do so was death. Sorry. The second thing we

10   definitely do is every event we adjudicated. And the

11   reason is sometimes a first event is rejected. So all

12   the events, when I show you multiple event

13   comparisons, are adjudicated. And far as is humanly

14   possible, the protocol pushed people to remain on the

15   drug.

16   DR. HARRINGTON: Terrific. That's very

17   helpful.

18   Mori?

19   MR. KRANTZ: Dr. Yusuf, a quick question,

20   any comments on systolic blood pressure? I know that

21   was a positive predictor in the sensitivity analysis,

22   and I think it's always germane to talk about blood

1   pressure with an anti-hypertensive. And I think were

2   there differences amongst the active comparators and

3   what role, if any, does blood pressure in the risk

4   reduction.

5   DR. YUSUF: Obviously, the combination had,

6   I think, a 2 and a bit blood pressure difference, 2.2

7   or 2.3 compared to telmisartan alone or ramipril

8   alone. But between telmisartan and ramipril, the

9   difference was only a 1 millimeter difference. And

10 when you do an adjusted analysis, which is there in

11 the sponsor's presentation and also in our New England

12 Journal of Medicine, it doesn't alter the conclusions.

13 There's hardly an effect on the point estimates. And

14 if they put it up for me here, it's essentially the

15 same results, both on the quadruple and the triple

16 endpoint point in both trials, ONTARGET and TRANSCEND.

17   But there's something we found very

18 interesting, which is not so much the adjustment for

19 blood pressure. It's a paper on observational

20 analysis on blood pressure that Peter Sleight just

21 published in Journal of Hypertension.

22   What we find is in this population. We

1 found it in HOPE, but we didn't publish because we

2 thought we were wrong in HOPE. It was that the shape

3 of the curve relating blood pressure to outcomes is

4 not very strong in this population except for strokes.

5 So heart failure, there isn't. For MI, there isn't.

6 And it's weak. It's there very weak. And this goes

7 to my pet thing, that in the elderly, the evidence

8 that below 160 to push blood pressure further down is

9 an extrapolation from the rest. But that's a

10 different argument. But for covariate adjustment,

11 it's not a steep relationship.

12   DR. KRANTZ: So, Dr. Yusuf, are you

13 referring to Eva Lonn's paper that looked at the

14 progressive decrement in effectiveness of ramipril in

15 the HOPE trial for stroke? Is that the paper?

16   DR. YUSUF: No, no.

17   DR. KRANTZ: It's not that it lost complete

18 significance, that it was all on the right side. But

19 for quartiles of blood pressure at baseline, it seemed

20 like the effectiveness in HOPE was diminutive.

21   DR. YUSUF: Actually, it was Jackie Bosch

22 that was the first author of that paper in the BMJ.

1   Is that the one that you're thinking about?

2   DR. KRANTZ: I don't recall.

3   DR. YUSUF: In that one in HOPE, there was

4   no significant heterogeneity. Remember, we've done in

5   each of these trials, hundreds and hundreds of

6   subgroup analysis. And so there wasn't significant

7   heterogeneity of the effects of ramipril on the

8   primary endpoint of CV death, MI, stroke. We've got

9   that in the main paper, and I can see my friend on the

10   other side agreeing. And the same thing with stroke

11   as well.   So I think the lack, the very

12   modest benefit, difference in blood pressure and the

13   lack of change of the results by adjustment and by

14   stratified analysis speaks to the fact the small

15   difference in blood pressure doesn't affect the

16   results.

17   DR. HARRINGTON: Other questions of the

18   advisory committee to either the sponsor or the FDA?

19   Sanjay?

20   DR. KAUL: I would like Dr. Yusuf to help me

21   understand the clinical meaningfulness of the pooled

22   estimate of the TRANSCEND and PRoFESS, the

  1 meaningfulness of the telmisartan versus placebo

  2 effect.

  3   What do you consider to be a clinically

  4 meaningful effect? We know it's a statistically

  5 significant and meets the criteria of p-value.

  6   DR. YUSUF: Okay. I think I first have to

  7 say I often don't get a chance to speak behind

  8 Sanjay's back. Now I do publicly. So thank you for

  9 that opportunity, Sanjay.

 10   [Laughter.]

 11   DR. YUSUF: I think the way to look at this

 12 is to say, look, you've got to take two things into

 13 account, the fact that in the meta-analysis of

 14 TRANSCEND and PRoFESS the mean follow-up is about

 15 three years. The first six months is heavily

 16 weighted, but that early post-stroke and the role of

 17 blood pressure lowering early post-stroke is just

 18 open. We don't really know.

 19   So in a sense, if I took a similar

 20 population and treated them, what would I do? I'd

 21 wait for the early post-stroke or the post-MI period

 22 to settle down and then treat. And then I wouldn't

1   just treat them for three years. I'd treat them for

2   five years.

3   So clinically, my judgment is much more

4   influenced by the post-six-month analysis than the

5   pre-six-month. We're talking how do I use the

6   information. And the post-six-month analysis is about

7   a 13 percent risk reduction. Taking everything into

8   account, it's about a 10 percent risk reduction. You

9   can choose which number you want.

10   In a low-risk population, that's not worth

11 it. In a high-risk population, especially if I can't

12 use an ACE inhibitor, to me, that's worth it. It's on

13 top of everything else. So that's the way I practice

14 medicine.

15   I have to say, before these results were

16 available, ONTARGET, TRANSCEND, I rarely used ARBs. I

17 rarely did. If my patients coughed, I pushed them to

18 continue on their ACE, telling them wouldn't you cough

19 and rather be alive than dead and stop coughing? Now

20 what I do is I avoid pushing them right against the

21 mat. I still start with an ACE, but now I say -- and

22 it's because of all these uncertainties we've talked

1   about. I know more about ramipril than I know about

2   the ARBs. So now I say I start with an ACE. Now, if

3   there is intolerance, I have an easier threshold to

4   move to an ARB.

5   So I hope I've answered your question,

6   Sanjay, both on the quantity of effect size I expect,

7   how I interpret the data and how I actually use the

8   data.

9   DR. KAUL: Salim, I'm going to push you

10 further on this.

11   DR. YUSUF: Sure.

12   DR. KAUL: Now, remind me what was the delta

13 that was used to power PRoFESS and TRANSCEND?

14   DR. YUSUF: Oh, I can tell you TRANSCEND

15 because I did it.

16   DR. KAUL: I can tell you what PRoFESS is.

17 I don't remember TRANSCEND. PRoFESS was 25 percent.

18   DR. YUSUF: Yes. I mean TRANSCEND was about

19 20 percent or so, about that. It was a little

20 discounted from HOPE, the 22 percent down. And

21 TRANSCEND was a very tough trial to recruit. I wish I

22 had the 8,000 or 9,000 we had in HOPE. But it was

1   like pulling teeth to do this trial.

2   DR. KAUL: So what was that delta based on?

3   DR. YUSUF: That delta was based on -- well,

4   there was no trial to go on. It was based on two

5   things. It was based on this is a clinically

6   important difference, not a minimally importance

7   difference and it is something that we would be able

8   to pull off.

9   I think all of us in trials know that a

10 trial design is a mixture of the ideal balanced by the

11 practical.

12   DR. KAUL: I agree. So if we assume that it

13 was 20 to 25 percent, what number would you choose for

14 me given the endpoints and given the disease as a

15 clinically relevant difference?

16   DR. YUSUF: I think there are two separate

17 issues. In an ideal world, if resources were

18 unlimited and there were lots of patients and you just

19 click a button and you can just recruit 10,000 people,

20 I would have liked to do TRANSCEND at 10,000 people.

21 Those who know me know that's absolutely truly meant.

22 But this is a very difficult population to recruit

1   with. That's why many people haven't done trials

2   intolerant to a drug. And we struggled to do this

3   trial, and we took six months longer to recruit and we

4   recruited 6,000. And we just couldn't do anymore.

5   Now, reverse it from that to say is 13

6   percent worthwhile? As I said before, 13 percent

7   definitely would not be worthwhile if you're talking

8   of very low-risk patients. But if you're talking of

9   people with an appreciable event rate, it is. Now,

10 maybe the example that comes to mind you won't like,

11 but I'll throw it up not because I'm a fan of it. And

12 it's the GUSTO trial, streptokinase TPA. You're

13 laughing because I've read your papers on it. But

14 that was considered to be meaningful. Bob will like

15 it.

16   DR. HARRINGTON: We like it.

17   DR. YUSUF: Yes. So in that, that

18 difference was considered meaningful enough to change

19 practice in the United States. So you take your pick.

20 I think 13 percent in a population with appreciable

21 risk is clinically important.

22   DR. HARRINGTON: Remember, GUSTO-I was

1 death, though.

2   DR. YUSUF: Yes.

3   DR. KAUL: If I can share my perspective on

4 this --

5   DR. HARRINGTON: Sanjay, before

6 you -- because that's going to, really, the essence of

7 what I want you to do next, which is start to share

8 perspectives on questions.

9   If I could just get people to ask the

10 questions now, if that's okay with you or is it an

11 extension of your question?

12   DR. KAUL: It is an extension.

13   DR. HARRINGTON: I'll grant you some

14 latitude here.

15   DR. KAUL: Okay. Thank you.

16   If you were to choose, for example, 15

17 percent as your clinically relevant difference, the

18 probability of a 15 percent difference in the pooled

19 trials is less than 5 percent. And if you were to

20 choose 13 percent, the probability's 11. And if you

21 were to choose 10 percent, the probability is about

22 37, 38 percent. Just to throw it up there.

1   I want to follow up this with another

2   question --

3   DR. YUSUF: Can I ask you a question of what

4   you just said?

5   DR. KAUL: Sure.

6   DR. YUSUF: How on earth did you get those

7   numbers? I completely disagree with that from an

8   intuition point of view. When you put all the data

9   together for, say, on the triple endpoint, especially

10 the post-six-months, you're getting a point estimate

11 around 12, 13 percent. That's the point estimate.

12 That gives you a 50 percent probability you would see

13 the 13 percent.

14   So how can you say it's 11 percent

15 probability? I'd like to understand that.

16   DR. KAUL: Well, I used the data that you

17 have in TRANSCEND, PRoFESS with the hazard ratio of

18 .92 going from .86 to .9 --

19   DR. YUSUF: Okay. But as I prefaced my

20 statement, that the PRoFESS and TRANSCEND part is

21 heavily weighted by the first six months of what

22 happened in PRoFESS.

```
 1          DR. KAUL:  Right, that's the data that I

 2   have.

 3          DR. YUSUF:  If you go to the next line,

 4   Sanjay, and you look at the .89 post-six-months and

 5   also take into account in post-six-months you only

 6   have two and a bit of years of follow-up in PRoFESS

 7   and TRANSCEND you have five years, then in a way, this

 8   analysis is weighting it against the reality if you

 9   assume the curves will diverge.  It's an if and if.

10          If you do that, I would say something in the

11   order of 11 -- this analysis --

12          DR. HARRINGTON:  Are you looking at a slide

13   there?

14          DR. YUSUF:  I'm looking at a slide.

15          DR. HARRINGTON:  Can we put it up?  There we

16   go.

17          DR. YUSUF:  So if you look at that

18   post-six-months, Sanjay, at the 13 percent or its

19   ratio of .87 post-six-months on top for the quadruple

20   endpoint and below for the triple endpoint 15 percent.

21   And then if you take, say, the bottom one because it's

22   easier for me to argue that one for the moment, .85,
```

1   the point estimate is that. That means that's the

2   expectation. So there should be at least a 50 percent

3   that's true if not higher because the p-value that is

4   higher. So I'm a little confused by the analysis you

5   did.

6   DR. KAUL: No, no. If you use this data,

7   the probability of the 10 percent difference is about

8   75 percent. The probability of a 13 percent

9   difference is about 40 percent.

10   DR. YUSUF: Which one are you using the --

11   DR. KAUL: 1286 divided by 12484, the 10.3

12   and 11.7.

13   DR. YUSUF: Okay. So I think -- can I

14   suggest that perhaps what you said is rephrased the

15   probability of a 10 percent effect is or greater is at

16   least 75 percent.

17   DR. KAUL: Right.

18   DR. YUSUF: Or greater. It's not 10 percent

19   precisely.

20   DR. KAUL: You're right.

21   DR. YUSUF: And the other one that you said

22   was, what is it, 13 percent was 40-odd percent or

1 greater. I think we are now on the same wavelength.

2 Thank you.

3   DR. HARRINGTON: Sanjay, just make sure that

4 for the panel that we all understand your point, that

5 what you're trying to get at is that in a variety of

6 estimates the effect that we observe in these trials

7 combined is a modest one. Is that your point?

8   DR. KAUL: That's the point I'm making, and

9 there's another larger point that I want to make is

10 that we should not reference our results to a greater

11 than zero percent effect, which is what the p-value

12 tells us. As a clinician, what I am interested in

13 knowing is I consider 10 or 15 percent to be a

14 clinically relevant difference. Tell me what the

15 likelihood of achieving that difference is. That's

16 all I care for. I don't care if it has thirty zeros

17 after the decimal points. It doesn't matter to me.

18   So that's what I'm trying to help

19 understand. What is the probability, the likelihood

20 of having a clinically relevant difference.

21   DR. YUSUF: I think the way Sanjay does on

22 this, not on all the other issues. And so in getting

1   to that answer, I take all the estimates I have. The

2   estimates I have are the direct comparisons, which is

3   in a population that's not the ONTARGET population. I

4   take the ONTARGET indirect putative placebo

5   comparison, which is a 21 percent estimate. How do

6   you formally mash it together is what's called a

7   network   meta-analyses, which I hate, so I'm

8   not going to do that. It has all kinds of problems.

9   But so I'd say the effect size is somewhere

10   in the 10 to 20 percent range. It could vary by

11   populations, but that's the range it is. So I don't

12   think any of us should focus on one number. So the

13   people not in ONTARGET, we're getting 10 to 15

14   percent. The people in ONTARGET, we're getting

15   estimate of 21 percent, discounted a bit if you want.

16   That's why I believe it's 10 to 20 percent. That's

17   the range.

18   DR. HARRINGTON: Fair enough. David?

19   DR. DeMETS: Yes, Dr. Yusuf, you have

20   focused a bit on the post-six-months period for the

21   combined analysis of PRoFESS and TRANSCEND. But the

22   first six months, they had ratios like 1.12. You

1 haven't commented. It's in the wrong direction and

2 not so far from being, quote, nominally significant.

3 Can you --

4   DR. YUSUF: David, it's a good point. The

5 entire excess in that analysis comes from the PRoFESS

6 trial, which is a very special period. There's no

7 excess in TRANSCEND, and that can be verified and I'm

8 sure the FDA may have checked it and can check it.

9 But that entire excess is coming from PRoFESS

10   Really there are concerns that blood

11 pressure lowering after a stroke may not be a good

12 thing. So I agree with you on that. And you know

13 what? I am taking that seriously and actually pushing

14 some other people to mount a study of a strategy of

15 blood pressure lowering early after stroke. Because

16 this is a relevant clinical question because soon

17 after a stroke, blood pressure's really high and the

18 theory is if you drop blood pressure, you may affect

19 autoregulation in the brain.

20   I think, David, it's a qualitatively

21 different period for strokes. It's not a

22 qualitatively different period for the TRANSCEND

1   population except that you don't expect treatment to

2   have kicked in so early with an atherosclerosis change

3   in treatment. I hope that's a useful answer.

4   DR. HARRINGTON: Okay. I'm going to look

5   around the room. Are there any further questions for

6   either the sponsor or the FDA?

7   Okay. Having heard that there are no

8   questions, let's now move into the questions that have

9   been asked of us. Some of this discussion we've

10 already had. For the panel members, in your packet

11 you should have the questions.

12   I am not going to read the prelude here

13 other than to state the opening sentence where

14 Dr. Stockbridge has asked us to "opine on the

15 approvability of telmisartan for use to decrease

16 cardiovascular events in patients aged 55 or older

17 with associated cardiovascular risk factors."

18   He goes on to give us an introduction, much

19 of, which we've talked about this morning, the basis

20 for the claim primarily being ONTARGET. And then to

21 get into a bit of the discussion around non-

22 inferiority, how it was constructed, the trial design

1   of ONTARGET using the HOPE data and then closing his

2   prelude with pointing out to us that the FDA process

3   for deriving the non-inferiority margin was as

4   described and as we've heard this morning.

5   Norm, before we launch into the questions,

6   do you have anything you want the panel to -- okay.

7   Go ahead, Bob.

8   DR. TEMPLE: Well, on reflecting and on

9   looking at it, one of the things that I don't think it

10 does, the questions do fully, is make the distinction

11 that I've been obsessing about between M1 and M2. So

12 one question one can ask is have we ruled out loss of

13 a significant fraction of the effect of ramipril. A

14 perfectly good question, it's the usual question we

15 ask.

16   A second question here, sort of hinted at by

17 Salim actually, is the question of whether there's

18 evidence of some effect, which might be relevant if

19 you wanted to use it in people who had been intolerant

20 of ABE inhibition. And you might think that the M1 is

21 more relevant to that. And there could be a

22 difference in how sure you are that you've ruled out

1   loss of M1 and how sure you are that you've ruled out

2   loss of M2, which is half of M1.

3   So I just think that should be kept in mind,

4   and we'll probably ask for that consideration as part

5   of number six. This is not to try to give everybody

6   an easy way out or anything like that. But it needs

7   to be considered because that is a possible use of a

8   drug like this.

9   DR. HARRINGTON: So, Bob, perhaps we can

10 have that discussion when we get to Question 4, which

11 is what should the non-inferiority margin be. And we

12 can approach it from the two direction of M1 and M2

13 and have the discussion at that point. Would that'd

14 be fair?

15   DR. TEMPLE: That'd be fine.

16   DR. HARRINGTON: Okay.

17   DR. TEMPLE: I'm just sort of flagging it

18 for thinking about.

19   DR. HARRINGTON: No, I think it's an

20 important discussion, and that's probably as I looked

21 through the questions where it might fit best. And

22 then it may cause us -- I hate the thought of altering

1   the final voting question, but it may at least cause

2   the panel to think about their comments when they

3   vote.

4   DR. TEMPLE: Right. It could be

5   incorporated into six. Six is, should it be approved

6   for general use. If that the answer to that were no,

7   a secondary question might be do you think it's

8   suitable for use in people who don't tolerate ACE

9   inhibitors.

10   DR. HARRINGTON: Would that be acceptable to

11 add that question?

12   DR. TEMPLE: Yes.

13   DR. HARRINGTON: Okay. So let's plan on

14 adding that question.

15   Okay. Just for a point of procedure, what

16 Elaine's asking me, if we're going to add a new voting

17 question, during the break, we'll insert that into the

18 voting system. Is that fair? Yes.

19   All right. So if we could, Elaine, put up

20 the first question for discussion and I'll read it.

21 I'll read the prelude, which is, "In HOPE, ramipril

22 was associated with 22 percent relative risk reduction

1 the primary endpoint of CV death, MI or stroke. This

2 finding included a 26 percent relative risk reduction

3 or 2 percent absolute in cardiovascular death, 20

4 percent relative reduction in MI, which was a 2.4

5 absolute reduction and a 32 percent risk reduction in

6 stroke, again, 1.5 percent in absolute terms. There

7 was a relative risk reduction of 16 percent, a 1.8

8 percent absolute for all cause mortality."

9   Question 1.1, as you see here that we'd like

10 to discuss, is, "In comparing a new treatment to

11 ramipril, is it sufficient to ensure that the new

12 therapy would likely have been superior to placebo

13 and, if so, on what endpoint?"

14   So who would like to begin the discussion

15 here? This gets a bit at the essence of what we

16 talked about this morning.

17   So go ahead, Ralph.

18   DR. D'AGOSTINO: I'd be happy to make a fool

19 of myself and start the thing.

20   When I look at these studies and going back

21 to the discussion this morning, I first worry about is

22 the active treatment showing itself to be superior,

1 and I'm sure that's embedded in here. So I want some

2 assurance that the active treatment is, in fact, has

3 assay sensitivity. And then I say you can then move

4 on to asking about the new treatment. And certainly,

5 I want it to be superior to the placebo by way of the

6 M1, M2 and the discounting without reliving all that

7 discussion.

8   But when you say is it sufficient to ensure

9 that the new treatment would likely have been superior

10 to the placebo, I'm talking about a very careful route

11 that takes you to an analysis that says you think you

12 have established the non-inferiority. And so at that

13 point, I'd say yes.

14   On what endpoint, I think that the endpoint

15 just can't be generated out of the blue, that it has

16 to be clinically meaningful endpoint. And these

17 composite endpoints, I'm not a big fan of putting in

18 congestive heart failure, hospitalizations, for

19 example, in the endpoint. So I'd like the endpoint to

20 be as meaningful as possible and as somehow or other

21 as consistent as possible in terms of how it impacts

22 on or how the drug impacts on it.

1   So I'm being longwinded, and I'm not trying

2   to avoid the question. But I think you can say "yes"

3   very simply and the endpoint should be meaningful, but

4   these are very hard questions to put forth. And I do

5   think we want the new drug to be superior. There's a

6   route we think that gets us there. And we do want an

7   endpoint that somehow or other if possible -- not

8   somehow or other but came from previous studies but

9   had meaning to it.

10   DR. HARRINGTON: So let me push you a little

11   bit.

12   Go ahead, Bob.

13   DR. TEMPLE: I just want to be sure I

14   understood. I'm sure Salim and the company would be

15   pleased to take the triple endpoint because they did

16   better on that. Are you saying that the fact that

17   that wasn't the primary endpoint doesn't worry you

18   that much because it's more reasonable?

19   DR. D'AGOSTINO: No, no, no, not at all. I

20   think that you -- I think what endpoint does the data,

21   the past data bear out is the one that you have data

22   on. And so that's the one that you have to go with.

1 But I think that a discussion about are the components

2 of that endpoint meaningful, I don't think you can

3 just say all our data is the 4-fold, now we're looking

4 at the 3-fold and we want to go with that.

5   DR. TEMPLE: Well, they chose the 4-fold

6 endpoint because they went back and looked at HOPE and

7 it won on that, too, and the hazard ratios were almost

8 the same. So there was a certain indifference there.

9   My own gut reaction is that I like the

10 triple better anyway because those are all tangible.

11 I'm not sure --

12   DR. D'AGOSTINO: And this is what I was

13 trying to say --

14   DR. TEMPLE: But it wasn't in this case

15 their primary endpoint --

16   DR. D'AGOSTINO: But I would --

17   DR. TEMPLE: -- how much you care.

18   DR. D'AGOSTINO: Well, but I'm saying that I

19 don't care for the congestive heart failure, but I'm

20 not that comfortable in saying that we can just

21 dismiss that piece because it wasn't dismissed

22 previously.

 1   DR. HARRINGTON: And I think that's going to

 2   be specifically one of the questions of moving from

 3   the quadruple to the triple.

 4   But, Ralph, I read something else into this

 5   question, which is that if you look at the HOPE

 6   results, it's actually the kind of trial that gives

 7   you a lot of comfort in composites because there's a

 8   great deal of consistency across all components. And

 9   one of the things I read into the question was in

10   order to compare something against ramipril if you

11   choose to use the composite, do you have to be really

12   consistent across all the components or do some of the

13   components matter more to you than others and is there

14   a way to consider that as you're thinking about this

15   study?

16   DR. D'AGOSTINO: Well, I think in generating

17   the endpoint, one comes up with the composite. And

18   the discussion in the HOPE trial could have been do

19   these components make sense, are they equally weighted

20   and so forth. I think when you move on to the non-

21   inferiority trial, you start asking that type of

22   question, it's in some sense a bit too late because I

1   think you have to go back to what the historical data

2   is. So if you start saying that I want to throw out

3   this component because I don't like it and so forth,

4   then where is the history? And I think that that --

5   you just can't suddenly start the game all over with

6   these   non-inferiority trials. I think you

7   have to go back to what the historical data says.

8   DR. HARRINGTON: To what you've already got?

9   DR. D'AGOSTINO: To what you have.

10   DR. HARRINGTON: But, David, this gets to an

11   issue that you had brought up a little while ago when

12   you said what would you be willing -- if someone

13   called you in the middle of the night, what are you

14   willing to trade off?

15   So now look at the HOPE results, you see

16   both the relative and absolute risk reductions here.

17   Are these the endpoints that matter because it's going

18   to get to the essence of how much of these specific

19   endpoints you're willing to potentially tradeoff.

20   DR. DeMETS: Well, I'm going to be fussier

21   on death, MI and stroke than death, MI, stroke and

22   hospitalization. I mean hospitalization, I don't want

1 to go there, but at least it's not going to give me

2 the same concerns if I'm giving up a lot on death, MI

3 and stroke. So in my mind, the criteria, that the

4 non-inferiority criteria changes once you throw in

5 something that's softer.

6   DR. HARRINGTON: So that leads us naturally

7 into the 1.2 and if people want to go back to 1.1, we

8 can. But your comment goes directly into this, which

9 is, "What portion of the benefit is it appropriate to

10 ensure that you've preserved and one, which of the

11 endpoints?"

12   Go ahead, Bob.

13   DR. TEMPLE: Well, I had the same question

14 for David. We spend a lot of time fussing about what

15 the specified primary endpoint was. And maybe we

16 overdo sometimes, I don't know. But I hear you saying

17 also that yeah, yeah, they specified the 4-part

18 endpoint but really the first three are so much more

19 important that you're not that horrified if one were

20 to focus on the 3-point endpoint. Am I reading you

21 right or reading you wrong?

22   DR. DeMETS: Yes, I guess in a superiority

1 trial I might argue differently or be a little harder

2 about it, but here it really is when you talk about

3 looking at the global picture. I mean in

4 non-inferiority, you kind of turn the whole table

5 upside down and you want to look at everything, right?

6   DR. TEMPLE: Okay. No, that's good. I'm

7 just checking. You are a statistician after all.

8   DR. DeMETS: Sometimes.

9   DR. HARRINGTON: Although he's trying to

10 retire, so.

11   So let's get, David, then to the essence of

12 the waking you up in the middle of the night call.

13 How much of the benefit do you believe has to be

14 preserved? And let's go endpoint by endpoint. Let's

15 do death, MI, stroke and let's do the composite.

16 You've already said you don't care so much about

17 rehospitalization. Well, you care about

18 rehospitalization, but not as much as the other three.

19 That's a value judgment. But let's go through the

20 other three.

21   DR. DeMETS: Well, I don't know that I'm

22 prepared to answer that. But clearly, death outranks

1 them all, and I would -- I don't have numbers to go

2 give you. But I would want to get a very little -- by

3 the way, we could put death in a composite for two

4 reasons. One, maybe we think it will change, but

5 also, it's a censoring nuisance. So some cases, you

6 might have no difference on death. That's okay, but

7 you don't want to get information censored out because

8 you don't believe that censoring is random

9 necessarily. But in this case, we believe that it has

10 an effect.

11   So anyways, mortality, I don't want to give

12 up hardly anything. The other two, well, I don't

13 know. It depends on what kind of MI, what kind of

14 stroke, I guess.

15   DR. HARRINGTON: Go ahead, Ralph.

16   DR. D'AGOSTINO: We should make sure that

17 it's CV mortality we're talking about.

18   DR. HARRINGTON: It's CV mortality that

19 we're --

20   DR. D'AGOSTINO: It's not just death.

21   DR. HARRINGTON: Although in the HOPE trial,

22 as you see the results here, there is a relative risk

1   reduction of 16 percent on all case mortality as well.

2   But what we're talking about in the endpoint is CV

3   mortality.

4   DR. D'AGOSTINO: Yes. So when we're judging

5   the components of the event, some people think the

6   consequences of stroke are worse than death and so

7   forth, so there's arguments in terms of what these

8   endpoints mean. If it was total mortality, it's

9   different than CV mortality.

10   DR. HARRINGTON: Go ahead, Bob.

11   DR. TEMPLE: All of the analyses that are

12 done are based on either the triple or the quadruple

13 endpoint. The ability to rule out anything on a

14 subset, a component of those is modest indeed. And

15 mortality was the smallest of them. So realistically,

16 with a composite endpoint, you never have a whole lot

17 of things in an equivalence trial about being sure

18 that you've lost this or that on that endpoint. If it

19 leaned badly the wrong way, you'd get nervous. But

20 the confidence interval on that single component of it

21 is very wide. And that's just always true.

22   DR. HARRINGTON: That's what I wanted to get

1   you to say, which was your qualitative statement that

2   the power for any of the individual components is

3   going to be limited. But you made the qualitative

4   statement that well, if it leaned the wrong way, it

5   might make you uncomfortable.

6   DR. TEMPLE: Right.

7   DR. HARRINGTON: Any other comments on this

8   Question 1.2?

9   Go ahead, Jonathan.

10   DR. FOX: Maybe just a brief observation

11 that might help put it into context for especially the

12 clinicians on the committee. The way I read this

13 question, I guess as Professor Yusuf and others have

14 made clear, if you size a trial infinitely large, you

15 can make an infinitesimally small difference from true

16 placebo statistically significant. But will it be

17 clinically meaningful, probably not.

18   So if thinking along those lines, my answer

19 to the first question would be no, assuming that you

20 were just looking at a very small numerical

21 difference. So then the second half of the question

22 becomes really relevant. And I just make reference to

1   the sponsor's Slide CE-66, which estimated the

2   clinical benefit of the actual direct placebo

3   comparisons that were done in the program of a

4   clinical benefit of somewhere between 8 and 13

5   percent. If we just take their data at face value,

6   maybe members of the committee want to look at that

7   and decide for themselves is that worth the effort or

8   is that an attractive choice considering some of the

9   other things we talked about today.

10   DR. HARRINGTON: Comments? Dr. Wolf.

11   DR. WOLF: Just a quick one on this question

12 about the waking up at 2:00 or 3:00 or 4:00 or

13 whatever your favorite time is and what would you not

14 like.

15   As Dr. DeMets said, in the randomized

16 placebo-controlled trial of TRANSCEND, there actually

17 was no difference in terms of cardiovascular death

18 between the drug and placebo. So at least in terms of

19 that most severe outcome in this placebo-controlled

20 trial, it didn't make any difference for that. It did

21 make a difference for some other things. It was

22 actually slightly worse for hospitalization for CHF.

1 Overall it was somewhat better, including all the

2 events. But this most serious one was actually a

3 wash. It was 140 CV deaths in the telmisartan, 137 in

4 the placebo, essentially the same.

5   But I think that the context of thinking

6 about the non-inferiority trial in answering either of

7 these questions is tempered heavily by this TRANSCEND

8 study. I think that looking at all of the HOPE plus

9 other studies, which you've randomized ACE inhibitor

10 versus a placebo, clearly except for the last one,

11 which we explained why it wasn't good. The other two,

12 it's clearly much better than the placebo, whereas in

13 this case, it is not clearly much better than a

14 placebo.   And so if we -- and a lot of

15 the time, particularly with antibiotics, we don't have

16 the advantage of having a placebo-controlled arm.

17 You've got essentially a non-inferiority study. Here

18 the non-inferiority study is informed by and I think

19 impacted enormously by the fact that they did for the

20 purpose of seeing how it would do on this group that

21 is intolerant to ACE inhibitors, they did this

22 placebo-controlled trial. I mean at the beginning of

1   the company's presentation, they said one of the

2   reasons for doing this is because there are a lot of

3   people who are intolerant to ACE inhibitors. So here

4   is the study on the people that are intolerant to ACE

5   inhibitors.

6   Clearly, the results are far -- you can play

7   them into having some subgroup advantage, but overall,

8   it was not statistically not better than a placebo.

9   And that's clearly a different output than you got or

10 outcome that you got from all these ACE inhibitor

11 studies. So I just think that weighs on the way we

12 think about this drug, the way we think about the non-

13 inferiority study and so forth.

14   DR. HARRINGTON: Dr. Krantz.

15   DR. KRANTZ: I guess maybe I might be

16 repeating myself, but I think when I read that

17 question I was sort of looking at the consistency of

18 the endpoint reduction across all the endpoints at

19 about 2 percent. And as I look at TRANSCEND, I mean

20 the highest risk reduction you have is 1 percent

21 absolute. So some of them go in the wrong direction,

22 some in the right, but none of them have that robust

1   absolute risk reduction to sort of Ralph's earlier

2   point about what's meaningful. I think, to Salim, he

3   mentioned a 15 percent relative risk reduction or a 10

4   percent is important to him, but I think at a patient

5   level, I think certainly the absolute risk reduction

6   certainly resonates more in terms of what's going to

7   benefit him or her.

8   DR. HARRINGTON: Other comments? Go ahead,

9   Ralph.

10   DR. D'AGOSTINO: Are we supposed to say what

11   proportion of them benefited?

12   DR. HARRINGTON: We're trying to work

13   towards that as to if there -- because this is going

14   to get into Bob's M1 and M2 question, which is given

15   the very important reductions in important endpoints,

16   death, MI, stroke, that are observed with ramipril,

17   what are you willing to give up of those very

18   important endpoints?

19   DR. D'AGOSTINO: I mean, I hope I've made

20   myself clear in terms of what I think of the endpoint.

21   I think you want the endpoint to be something that is

22   historical and you look for the consistency, but

1   you're not going to get winners in each of the

2   components.

3   So all of that said, now in terms of what

4   proportion of the benefits is appropriate, I don't

5   know what the answer to this is. And you hear 50

6   percent pulled out and you hear discounting and so

7   forth, which all sounds even to a statistician, simple

8   statistician like myself, to be very magical.

9   I think the thing that drives me is that

10 what kind of data do you have. And I'm not saying

11 anything new. We've heard it all day. But if you

12 have lots of previous studies, you have lots of

13 comfort in terms of what you expect to see. You can

14 zero in very quickly. If you have one trial and

15 there's differences somewhat about the population,

16 things of this nature, but even if it's the same

17 population but a different drug, you're less apt to be

18 willing to say that one trial informs you a lot. So

19 you have to play the game of doing some discounting

20 and doing some preservation.

21   I think the procedure that the FDA was

22 mentioning today is a reasonable thing to do. Look at

1   the confidence interval. Do some discounting on that,

2   and that would basically be sort of the final M1 type

3   of thing where you -- here's where you start with the

4   difference and you've made some modifications. I

5   think that's reasonable.

6   I don't know what sort of the clinicians

7   would say with that. I think you have to take that

8   number and ask is it clinically meaningful. And I

9   didn't really a decent discussion of that today.

10   DR. HARRINGTON: Well, let's have that

11 discussion. Go ahead, Bob.

12   DR. TEMPLE: Remember the history here.

13 Leaving aside the question of what the M1 should be,

14 we concluded that M1 was about 16 percent except we

15 had some nervousness about the two other trials maybe

16 making that a little excessive. But we didn't have

17 those when we originally did it.

18   So I think whatever M1 you pick, the basic

19 conclusion is -- unless you really believe there's no

20 evidence ramipril has any effect at all, which I don't

21 think anybody believes -- they probably have been able

22 to show in the non-inferiority study that it's better

1   than nothing. That was what our debate was about.

2   Our debate is whether it showed the 50 percent

3   preservation.

4   Now, Sid raises the additional question that

5   apart from the non-inferiority study, there's another

6   piece of information. And that's the PRoFESS,,

7   whichever it was,, which is sort of borderline but

8   does not show clear success in a study that's decent

9   sized. It's still 6,000 people, and so you have to

10 factor that in, too.

11   But this question was really how do you rank

12 those things, which is, is it good enough to show that

13 it's better than nothing for, which there's at least a

14 fair amount of evidence if you don't look at the

15 placebo-controlled study. And then if you don't think

16 just showing better than nothing is good enough, do

17 you like our 50 percent or what percent should it be?

18   Is that a fair summary, Norm?

19   DR. STOCKBRIDGE: I guess I'd like to point

20 out that had they won on a placebo-controlled trial,

21 we would not be asking how it compared with other

22 therapy. For major outcomes, we would have bought any

1   effect size whatsoever. So this question of is it to

2   small to care about would never have arisen. So I

3   guess partly you're invited to say why particularly

4   you care about preserving more than zero percent in a

5   non-inferiority setting.

6   DR. TEMPLE: There's some irony in that, of

7   course. If you can manage to do a placebo-controlled

8   trial, then as Norm says, we don't even ask how you

9   compare because you have no way of getting at it.

10   But in the situation where the accepted

11 therapy is so good you really can't do a

12 placebo-controlled trial, then we say you better

13 preserve more of it than some. But of course, in

14 people who can't tolerate a drug, Norm would perhaps

15 argue that you're closer to the first date.

16   DR. HARRINGTON: And that was essentially

17 what the FDA reviewers walked us through this morning,

18 that if you're not convinced that there is superiority

19 over placebo, how do you start approaching the

20 question? And I'm not sure that everyone agrees that

21 there's no effect there despite looking at all of the

22 data this morning.

1   I agree with you, Bob.

2   Go ahead, David.

3   DR. DeMETS: I'm not sure this is relevant

4   to the question, but let me say it anyway. If I were

5   to figure out what should the margin be, we can argue

6   all day and the rest of the week about what the

7   methodology should be. But it's clear that we have

8   one study, a really well done study, but it's only one

9   study. So maybe the point estimate is giving just a

10 little bit too much emphasis to that point estimate

11 because of all the reasons I alluded to this morning.

12   So you want to be conservative in some way.

13 So you pick the lower confidence rule. You go into

14 the math, and you get an answer of 1.08. But then you

15 realize that they can't do that study.

16   DR. TEMPLE: 1.16 for M1, that's what we

17 get, 1.16, not 1.08.

18   DR. DeMETS: But you determine it by --

19   DR. TEMPLE: 1.18 is preserving half of

20 that.

21   DR. DeMETS: Right, right. So you go

22 through that. When I wake up in the middle of the

1 night, I probably wouldn't choose 1.13 either. It

2 seems to be too generous.

3   Before I got deep into this, I sort of

4 though what would I pick for this endpoint. And I

5 said oh, about 1.1. And then I looked at the results,

6 and I said oh, damn.

7   So the point is that you have to balance it

8 between practicality and what you'd like to have. And

9 it's very easy to drive that margin down so far that

10 we're done. It doesn't take too much.

11   DR. HARRINGTON: I think Dr. Yusuf made the

12 comment this morning that going from the .08 versus

13 .13 is about the doubling of the sample size. Is that

14 what you had said?

15   DR. YUSUF: Yes.

16   DR. DeMETS: It is a statistical question up

17 to a point, but in the end, it comes down to what's a

18 clinically, where do you draw the clinical. And it's

19 a judgment and nobody likes that, of course, because

20 it's harder, but I don't see how we can escape that.

21 Because if we put on our statistical hats and get

22 really rigorous, we can go home. It's over. But if

1   we say what's the balance, that's a tough problem. So

2   that's where I start out before I got deep into this,

3   and I guess I'm still there.

4   DR. HARRINGTON: Sanjay.

5   DR. KAUL: Well, that brings me back to what

6   I was trying to have Salim persuade us as to what is a

7   clinically relevant margin. And to answer your

8   question about 16 percent, if I heard Salim correctly,

9   I think I heard somewhere between 10 to 20 percent

10   with a 13 percent was your emphasis.

11   DR. YUSUF: I did some calculations here.

12   Can I --

13   DR. HARRINGTON: Go up to the microphone so

14   we can here you.

15   DR. KAUL: So if 13 percent is a clinically

16   important difference, then should the boundary be

17   larger than that or smaller than that? And to my

18   mind, the boundary should be smaller than that. And

19   you cannot exceed that harm. So is that something

20   that --

21   DR. TEMPLE: Well, we have this conversation

22   all the time. Remember, in order to prove things, we

1   take a conservative posture. We use a p of .05. We

2   use the 95 percent lower bound. That is not the only

3   measure of the effect of the control. It's not the

4   only measure of the comparison in the non-inferiority

5   study. So because we're taking conservative

6   postures -- this is my interpretation anyway -- we

7   accept some willing -- we accept an M2 of, say, 50

8   percent of M1 is. You don't really think you've lost

9   50 percent of it, and the point estimates are usually

10   on top of each other. But that's what we're ruling

11   out with our usual degree of assurance.

12   That's not the same as being the best

13   possible measure of what the effect is, and I'm not

14   sure how to put that together. But we grapple with

15   this all the time, so anyway.

16   DR. KAUL: So the question remains, Salim,

17   should we be on the right side of 13 or on the left

18   side of 13?

19   DR. YUSUF: On top of 13. I've been

20   thinking during this discussion, which I found

21   enlightening. If you take the M1 concept, Bob, and

22   you say 16 percent clearly, the ONTARGET study met. I

1   completely by   Dr. Wolf said, you cannot look at

2   ONTARGET on its own. You've got to look at the rest of

3   the data, although I think all of us recognize that

4   the superiority trial was done in a different

5   population. I think we recognize.

6   So what we're saying is I'd like to see a

7   signal of superiority, and I think that's perfectly

8   fair. That was the thinking when we designed the

9   study. Dave comes to the point, look, I'm much more

10   comfortable with a triple endpoint. If you take the

11   triple endpoint, TRANSCEND is nominally significant,

12   13 percent reduction.

13   Then if you do multiple events, which, Dave,

14   through the thing, we're obliged to look at the whole

15   thing -- well, the whole thing is not just the first

16   events. It's all events. When you get that, you

17   actually get -- again, you get 13 percent. If you

18   look at cardiovascular hospitalization, you're in the

19   same ballpark.

20   Something is telling me in the TRANSCEND-

21   type population, the real estimate is around 13

22   percent. Maybe in the ONTARGET-type thing, you

1   discount the 21 percent because of what we imputed by

2   two-thirds or three-quarters by a quarter or a third.

3   That is the 66, 75 percent. That is a 15 or 16

4   percent. I think Bob's 16 percent is there.

5   So the 13 percent is not that different from

6   the 16 percent. So ONTARGET population, about 16

7   percent using the confidence limits thing, the

8   non-ONTARGET TRANSCEND -- remember these are people

9   who can't tolerate an ACE. Using the superiority

10 comparison and all the events on the triple endpoint

11 is telling you 13 percent. Well, that is a zone of

12 comfort that I as both as a methodologist and as a

13 statistician actually truly believe the treatment

14 effects are.

15   I completely agree with Dr. Wolf. You've

16 got to use both trials, not just one trial. Each

17 trial informs the other, but you use it as a continuum

18 of evidence. So hopefully, I've answered your

19 question. I really feel very comfortable that the

20 real effects is in the 13 to 16 percent range.

21   DR. HARRINGTON: So let's go to Ralph and

22 then Emil.

 1   DR. D'AGOSTINO: Well, I was going to say

 2   what David and I are trying to say, we can do the

 3   mathematics, but at the end of the day, you get a 1.16

 4   or a 1.08. And I haven't heard anything to say how

 5   you select over that. It's not a comfort to me to say

 6   I think from the data that it looks like it's 1.16

 7   because 1.16 may not be clinically meaningful. And so

 8   how do you make that jump? How do you bring in the

 9   clinical and take it away from just the statistical

10   computation?

11   Because again, when I started with the

12   discussions with the FDA years about the percent, we

13   used to talk about 80 percent and then it moved to 50

14   percent and so forth, at least in some of my

15   discussions. I have a biased set of discussions. But

16   why 50 percent down to 1.08? Why not some other

17   number? So how do you look at the data and say it's

18   clinically significant?

19   Though I admire all the analysis that was

20   done, I don't take comfort in saying I looked at the

21   data afterwards and I see some consistency that comes

22   out to 1.16. That's not the answer I'm hoping to

1 hear.

2   DR. HARRINGTON: I think that Dr. Pfeffer

3 alluded to some of this this morning, Ralph, as that

4 this whole notion of ACE intolerance is while cough

5 may sound like a trivial problem, it really does take

6 people off of a medication, which might be very

7 valuable for them. And so it's a real clinical issue.

8   So then the question you ask yourself, I

9 think most of us do just what Dr. Yusuf described,,

10 which is that you work real hard to keep people on ACE

11 inhibitors but at some point you need another path.

12 And so then I think the question that's really

13 unsettled is above 50 sounds reasonable, 100 sounds

14 well, that's awfully tough and it somewhere in the

15 middle.

16   I think that the discomfort we're all

17 getting around is that if we were preventing

18 rehospitalization, I might say well, 50 percent is

19 probably good enough. But we've got the ramipril

20 data, which are pretty compelling for pretty bad

21 events, death, MI and stroke. And so now I'd like to

22 be closer to 100, and so is it 66, 75? I don't know

1   exactly what that answer is.

2   DR. D'AGOSTINO: And I do want to also

3   emphasize I don't mind you clinicians surrendering to

4   the statisticians. I'd like to just give you a chance

5   to not have to do so.

6   DR. HARRINGTON: I'll call you on my way to

7   the cath lab tomorrow morning.

8   DR. TEMPLE: I don't know whether it's

9   appropriate to even mention practical things. Maybe

10 the answer to this is someone would say well, just

11 beat the other drug. But as a practical matter when

12 you try to assure retention of much more than 50

13 percent, you often find you can't do the study at all.

14 So I mean someone could say well, big deal, so I won't

15 have another drug.

16   In this case, there is at least some reason

17 to wish you did have another drug. And I would make

18 the observation that sometime you find things later

19 that you didn't know. It's not a bad idea to have

20 more than one drug approved. It's really only

21 ramipril that's got the approval for this.

22   DR. HARRINGTON: I think you're bringing up

1 two very important points, one of, which is I doubt

2 there's a clinician around the table that doesn't want

3 to have another choice because this is a real problem

4 of people not being able to take ACE inhibitors.

5   I think you're making the same point that

6 David's making, which is there is a practical barrier

7 here that it's easy to say well, set it at

8 such-and-such, but if you can't do the trials, well,

9 that doesn't help us, either.

10   DR. TEMPLE: The other thing, there have

11 been various estimates given, .16, .08 and stuff like

12 that. We got to remember what each of those is. The

13 results of some of the trials give a point estimate

14 and a confidence interval. When we say .16 as M1,

15 then if you show that you've ruled out loss of all of

16 that, which is what our statistical test does, you

17 haven't shown that you've preserved 1.16, you've shown

18 that you haven't lost all of it and you've preserved

19 something.

20   It's true when you go to 50 percent, then

21 you feel comfortable that you've preserved at least .8

22 percent of the ramipril effect. We're just putting a

1   lot of numbers out.

2   Now, Salim is making the case that the best

3   estimate for some of these things is more in the

4   neighborhood of 13 percent, a hazard ratio of .13,

5   fine. That's a different question, though.

6   DR. HARRINGTON: I think that's actually a

7   pretty good summary.

8   Emil, you wanted to jump in here?

9   DR. PAGANINI: Just a quick thing, if you

10 eliminate the idea of the non-tolerant patient and

11 just take all patients, you're really looking at an

12 ACE and an ARB, so there are two different classes.

13 They do the same thing. They may be generally the

14 same, but they're two different classes.

15   If you do that and then you further

16 eliminate hospitalization, which I think was a big

17 mistake on the sponsor's part to do because it's so

18 variable and we've heard from Jim that it was very

19 variable despite all of the things. So you just go to

20 the three effects that with comparative trial that

21 they did in ramipril, then it meets everybody's

22 criteria. So it could be an alternative to an already

1   accepted drug and treatment so that's a good thing.

2   But then you go to the prospective trials

3   where you have a placebo control, and you're starting

4   to look at placebo in your drug, whatever drug against

5   no drug. And then you become a little bit less

6   impressed with it. In the PRoFESS trial, okay, well,

7   you're really dealing with a lower blood pressure,

8   it's a different thing. You're looking at early

9   strokes. Nobody's done that, probably bad idea, et

10 cetera. So all right, so you throw that one out.

11   Now you're left with TRANSCEND. So

12 TRANSCEND said okay, now I'm just going to take care

13 of the people who have an intolerance to an ACE

14 inhibition. In there against the placebo, in there

15 you get about a 13 percent reduction, plus or minus,

16 not that impressive.

17   So is there a signal there at all for that

18 subpopulation that would then allow you to consider an

19 M2 because it's so impressive? But you don't really

20 need to because you've already met your primary, if

21 you take out hospitalization. So that's where I'm

22 having a problem. I mean, I'm adjusting data to come

1 up with a solution. And I see the company has done

2 the same.   And I think we're in a

3 conundrum here. I don't see a big effect in the ACE-

4 intolerant patient. There is an effect. It is

5 statistically significant. Is that better than

6 nothing, 13 percent? But if you then go back and you

7 take a look at -- so you say well, that's 13 percent.

8 What are you going to do, throw these guys out? 13

9 percent doesn't carry. It's an effect. Okay, it's an

10 effect. But it's not a major effect to allow for a 50

11 percent reduction effectiveness in the other groups.

12   So I'm -- but he made it. So it made the

13 prior FDA bottom line if you take the fourth issue,

14 which is hospitalization out, which is so subjective.

15   DR. TEMPLE: I just want to be sure we

16 understand. You're saying arguably at least the

17 non-inferiority study preserves the HOPE margin and

18 that looks pretty good and that would argue for that's

19 being okay. But now you go look at TRANSCEND and what

20 you thought might have been true looks a little

21 weaker. It doesn't look as if it's as big an effect.

22 Is   that --

1   DR. PAGANINI: (Affirmatively nods.)

2   DR. HARRINGTON: I think that's exactly the

3   challenge that we're going to build up to here. So

4   let's -- I think we've had a good conversation, Norm,

5   about this question about the different endpoints.

6   But I think the next question starts getting into some

7   of the issues that Bob O'Neill earlier this morning

8   about what does it mean when you have a single study,

9   then new information becomes available, which is going

10   to be Question 3 and how we start to put that

11   together.

12   So let's go to Question 2. And the panel

13   can see the question here. "In non-inferiority

14   testing, there are various strategies intended to

15   ensure that the new therapy would likely have been

16   superior to placebo. How did the sponsor's strategy

17   address" -- and let's -- we'll throw them all out

18   there. And you can start at the beginning or bring

19   them all into your answer.

20   But we want you to somehow comment on the

21   use of a single reference study. So how much

22   confidence do you have in HOPE as a single reference

 1   study, the choice of the endpoint from HOPE, so this

 2   gets into the issue as Ralph has already brought up

 3   the triple versus the quadruple. Something that we're

 4   going to need David's help and Ralph's help thinking

 5   about, the early termination of HOPE. Professor Yusuf

 6   addressed the stopping rules in HOPE this morning, but

 7   we haven't had any discussion around that yet and what

 8   that means for what the observed effect actually was.

 9   And the evolving treatment for high-risk patients,

10   which we've already started talking about, anti-

11   platelet therapy, beta-blockers, statins, et cetera.

12   So who wants to kick us off here thinking

13   about this question and how the sponsor began to

14   address these issues? Sanjay, you want to kick us off

15   here thinking about single reference study?

16   DR. KAUL: Well, they didn't have any other

17   options. I mean, there was the only study at that

18   time unless you consider ACE inhibitors to be a class

19   effect and then you could have borrowed on the

20   previous evidence. So I think they did not have many

21   choices, number one.

22   Number two, I would have liked to have seen

1 a more conservative estimate. I think what they did

2 was essentially appoint estimate based choice, and I

3 would have liked to have seen some accounting for --

4 I'm not going to use the word "discount" -- some

5 accounting for the variance, which clearly would have

6 entered into the scheme if they had many other trials.

7   DR. HARRINGTON: You prefer the more

8 conservative FDA margin as described this morning?

9   DR. KAUL: Yes.

10   DR. HARRINGTON: And as we talked about this

11 morning, obviously, you can only work with what you've

12 got, and they had HOPE. They had another long history

13 of ACE inhibitor trials. But as the FDA reviewer

14 pointed out this morning, those trials are different.

15 They're heart beat dysfunction. They're post-MI, et

16 cetera. So it's okay to have used HOPE only here?

17   DR. KAUL: Yes, it's okay to have used HOPE,

18 but I would have liked them to have a more persuasive

19 argument for doing what they did for their estimation

20 of the margin.

21   DR. HARRINGTON: So, David, let me jump to

22 you because this gets to Question 2.3 here, which is

1   the early termination. And one of the questions that

2   always emerges when a trial is stopped early because

3   of benefit is that you're seeing the extreme benefit

4   because it surpasses an early stopping rule. Dr.

5   Yusuf explained to us this morning what the stopping

6   rules were and implied that they were pretty

7   conservative. And so we can feel confident in this

8   effect as being potentially a reliable estimate of the

9   true effect. Do you want to comment on that?

10   DR. DeMETS: Sure. Well, obviously, if you

11   stop a trial early because of benefit in this case,

12   you know you can show mathematically that you were

13   probably on a random high. And so statisticians have

14   worked on methods to adjust the estimate that you

15   obtain back towards the null hypothesis by some

16   amount. Now, if you use a conservative boundary such

17   as the one that was proposed or perhaps commonly used

18   as an alternative is the O'Brien-Fleming boundary,

19   those type of boundaries, the adjustment is small in

20   comparison to other boundaries that one might have

21   chosen like a Pocock-type boundary, for example.

22   So I would have been happier if the

1 calculation had been done, but my guess is it would be

2 modest if you did it. So it's probably not a 22

3 percent reduction. Maybe it's 21. Maybe it's 20. I

4 don't know. It's in that neighborhood probably, but

5 it's not a major change.

6   DR. HARRINGTON: So when you say that it was

7 a random high, what Dr. Yusuf went through with us

8 this morning is that he said look, in 1996, it was

9 already exceeding the stopping boundaries. A year

10 later, it's still exceeding it, and we waited still

11 another six months to see if it exceeded it. Does

12 that give you more confidence?

13   DR. DeMETS: All those things help you say

14 it wasn't just a spike that day, but it still could be

15 a run.

16   DR. HARRINGTON: Let me go to Ralph and then

17 Mori.

18   DR. D'AGOSTINO: I agree with that, and I

19 think the way it was presented was quite conservative.

20 But I want to take this opportunity to say that when

21 these studies stop early, I do not think that people

22 making presentations at the American Heart Association

1   and the American College of Cardiology should count

2   the numbers of zeros between the decimal point and the

3   1 in the p-value. The place where you really are

4   overdoing is the reporting of how significant the

5   results are. It may that there was an overestimate in

6   the effect and so forth in this one that we saw today

7   sort of -- and the fact that they kept looking was if

8   there was a spike, they would have probably seen it,

9   and they didn't. So it's probably quite reliable.

10 It's how significant you think your results are that

11 sometimes gets people to get carried away with, and

12 that doesn't enter into this discussion actually.

13   DR. DeMETS: You can actually adjust the

14 p-value, too, by the same methodology.

15   DR. D'AGOSTINO: Exactly,, which they

16 oftentimes don't.

17   DR. HARRINGTON: Bob and then Mori.

18   DR. TEMPLE: So, Ralph, were you advocating

19 just, say, a p less than .05 and leave it at that or,

20 well, that the alternative is to do one of these

21 adjustments? Because --

22   DR. D'AGOSTINO: The adjustment, there are

1 ways of doing it formally and you can just do it,

2 right.

3   DR. TEMPLE: That seems better because

4 otherwise I mean --

5   DR. D'AGOSTINO: What I'm --

6   DR. TEMPLE: If you stop early, it's because

7 the effect was spectacular.

8   DR. D'AGOSTINO: I'm going on a tangent, but

9 I see here over and over again, the p was .00001 and

10 the cheers come up from the audience and so forth, and

11 I think that's just bad science.

12   DR. TEMPLE: Right. Does the fact that they

13 went within six months of when they were going to quit

14 influence your view at all? I mean, they almost

15 finished.

16   DR. D'AGOSTINO: Say that again.

17   DR. TEMPLE: They almost finished in time.

18   DR. D'AGOSTINO: Exactly.

19   DR. TEMPLE: And that matters, doesn't it?

20   DR. D'AGOSTINO: I mean, I was surprised

21 that they were moving and just kept looking and

22 looking and looking because usually, when I'm in the

1 situation, you pull in all the data and so forth and

2 make sure you gather all the data that's out there and

3 do another analysis just to be comfortable. But here

4 they kept looking at it, and I think that was a very

5 good move and something that gives us a lot of faith

6 in what they ended up producing.

7   DR. HARRINGTON: So that I think is the

8 essence of what Norm wants us to get to is that if we

9 only had a single study as we talked about, Ralph and

10 David, you guys are pretty comfortable that the

11 methodology that they used in terms of the stopping

12 give us some measure of reliability that that was

13 likely the true effect. I mean, it was late in the

14 trial, so most of the information had already been

15 gathered. They looked at it over time. They made

16 sure it was not a random spike. So what we've

17 observed from HOPE is a pretty reliable estimate.

18   DR. D'AGOSTINO: I guess also, David, is if

19 they didn't do all these things, they would ended up

20 with an estimate that's quite large in terms of the

21 effect they're looking for. So all the things they

22 did was going to sort of usually diminish the effect.

1   And so if they were to -- if they went sledgehammer

2   and they stopped -- not sledgehammer but they went

3   with the elegance of their mathematics and stopped

4   right away, there probably would still be argument

5   that maybe it's too big an effect they're looking at

6   as opposed to --

7   DR. HARRINGTON: That's an overestimation of

8   the true effect.

9   Go ahead, Bob.

10   DR. D'AGOSTINO: And but then that impacts

11   on their non-inferiority because they live with that

12   overestimate.

13   DR. HARRINGTON: Correct.

14   Bob.

15   DR. TEMPLE: Well, maybe this is the same

16   thing as I asked before, I've never quite understood

17   this, though I recognize everybody worries about

18   random highs. If you are looking at events that

19   occurred during a given period, that I understand why

20   a random high might get you excited. But when you're

21   looking at cumulative data where you have 90 percent

22   of the data and now you're adding 3 percent, how

1 susceptible to a random high is that?

2 　　　　DR. DeMETS: It's not. First of all, you

3 had a conservative boundary that allowed you to get

4 that far in this trial. So those effects all get

5 minimized in whatever adjustment. If you did go to

6 the trouble of adjusting it, it would be modest

7 because of that. So your intuition is correct. It

8 will be something, but it will be very small.

9 　　　　DR. HARRINGTON: Most of the information was

10 in by the time it was stopped.

11 　　　　DR. TEMPLE: You have to use intuition if

12 you don't know anything.

13 　　　　DR. HARRINGTON: Go ahead, Mori.

14 　　　　DR. KRANTZ: Just real quick, I think there

15 is data from the HOPE II trial that the curves

16 continued to separate. So I think we're pretty

17 confident in that aspect. I think that was published

18 again, maybe the Eva Lonn.

19 　　　　But I guess this is kind of a dumb

20 statistical question, but sort of springing off of

21 what Emil said, he was mentioning the .87 in the other

22 placebo-controlled trial in TRANSCEND. So not being a

1   statistician, why not take the inverse of that for

2   your M1 and discount that by half? That would be .17

3   and then you would go down. Maybe I'm just --

4   DR. HARRINGTON: Remember, they didn't have

5   that knowledge when they planned ONTARGET, and that

6   was my question to Bob O'Neill this morning. Is how

7   do you then think about that when new data becomes

8   available during the course of the trial? But when

9   they planned it, they didn't know.

10   Go ahead, Dr. Wolf.

11   DR. WOLF: This is just a slight elaboration

12   or adding to what Sanjay was saying, which is back to

13   this first question here. Let's assume instead of

14   having just HOPE metaphorically, there were five

15   trials instead of one in the beginning when this was

16   planned. In that case, it might have made sense to use

17   a point estimate.

18   But I think that the FDA has sort of hinted

19   at this. The very reason they felt they needed to use

20   the lower bound of the 95 percent confidence interval

21   is that there was only one study. And so that the one

22   study really drives how you set up the non-inferiority

1 margin. And that was the basis as a way, the

2 difference of opinion between the FDA and the company.

3 Again, we go back to this. You only had one study

4 then, you can add these other studies afterwards. But

5 that's why I think they had to stick to this lower 95

6 percent confidence margin.

7   DR. HARRINGTON: Bob O'Neill, is that an

8 accurate reflection?

9   DR. O'NEILL: Yes.

10   DR. HARRINGTON: Let's look at the 2.2 and

11 2.4. Well, 2.2, we've sort of talked about. People

12 seem to prefer -- and I'm not going to get into

13 whether or not you can look at the triple because

14 you've already you've already failed on the quadruple.

15 But let's just say you were picking the endpoints at

16 the beginning. It sounds as though the group prefers

17 the triple of CV death, MI stroke and that the

18 hospitalization, while important, seems less

19 persuasive. Fair statement?

20   DR. KAUL: Well, I'm of the opinion that we

21 should do exactly what we say and then say what we do.

22   DR. HARRINGTON: We're going to come to

1   that, which is the testing of the quadruple and then

2   moving to the triple. No, no, no. That's what I say,

3   Sanjay, I just want to make sure that people separated

4   those two questions.

5   Would you prefer, Sanjay, a composite with

6   the three components I mentioned or the four

7   components if you were starting afresh?

8   DR. KAUL: Well, it depends on what the

9   components are. One of my pet peeves about clinical

10 trials is the use of composite endpoint. Just like

11 you can prove anything with statistics only if you use

12 them improperly, you can always prove anything with

13 clinical trials if you use your composite endpoints

14 carefully.

15   So it all depends on what the components

16 are. And I agree that admission for hospitalization is

17 a subjective endpoint. I don't want to call it soft

18 endpoint because it certainly has an impact on our

19 healthcare budget. It constitutes one of the

20 principal reasons for our hospital-based expenses. So

21 I would prefer endpoints to be robust and preferably

22 include mortality because of competing risk and

1 include endpoints that are irreversible morbidity. So

2 as a general statement, yes, cardiovascular death, MI

3 and stroke meet that criteria.

4   DR. HARRINGTON: Go ahead, Dr. Wolf.

5   DR. WOLF: Just looking at the time curves

6 again in TRANSCEND, if you look at the 4-fold

7 endpoint, which is again the primary endpoint that was

8 chosen by the company, up until roughly Day 1250, the

9 placebo is actually better. And then it starts

10 diverging a little bit. But so the point is that the

11 drug did much better on the 3-fold endpoint than it

12 did on the 4-fold, the one that was chosen. And this

13 is again a   placebo-controlled trial where it's

14 only after three or four years that you're getting

15 some benefit of the drug over a placebo and the

16 difference being that fourth endpoint, hospitalization

17 for CHF.

18   DR. HARRINGTON: And I think that that time

19 issue is something that Dr. Yusuf brought up a few

20 times.

21   Norm, did you have a comment?

22   DR. STOCKBRIDGE: Well, I wanted to note

1   that there was a perfectly rational choice of

2   employing the 4-component endpoint out of HOPE. That

3   was not -- it's only because it didn't seem to work

4   out so well that we're smart enough today to say gosh,

5   we shouldn't have done that. They had perfectly good

6   reason to do that.

7   So the point of that question really is if

8   you're now going to pay attention to the 3-component

9   endpoint for some reason, what is it -- how do you --

10   I have to use the word discount. How do you discount

11   the fact that you've had to go ignoring the 4-

12   component endpoint in order to get a chance to

13   consider it? Yeah, I apologize for the word discount.

14   DR. HARRINGTON: So you're asking the

15   question, Norm,, which I think the FDA reviewers

16   brought up, that if you fail on the quadruple, do you

17   even make it to the triple? Is that your question?

18   DR. STOCKBRIDGE: There are places here

19   where various people are trying to figure out how to

20   put things together. And certainly, the paradigm

21   that's most familiar to us is the one that has the

22   properties that are best understood are ones where we

1   actually pay attention to the p-values --

2   DR. O'NEILL: Pre-specification.

3   DR. STOCKBRIDGE: -- pre-specification,

4   right. People are inclined to drift away from that

5   here at their peril. So this is one of the places

6   where people are paying attention to an endpoint that

7   wasn't the primary. Does that affect your confidence

8   in what you're doing at all?

9   DR. HARRINGTON: It's an interesting

10   question, isn't it? Because in HOPE, the primary

11   endpoint was the triple, but as you observed, that

12   when they added the CHF hospitalization in, it was

13   consistent with the overall thing. And so in order to

14   increase the composite for the next trial, they added

15   it in. But one could argue that in HOPE, that may

16   have been the flawed secondary endpoint that then gets

17   added in the second time around. So where the truth

18   is, I don't know. But your point about quadruple and

19   then stopping is not a trivial one and we are going to

20   come to that.

21   Go ahead, Bob, and then Emil.

22   DR. TEMPLE: The endpoints that you study

1   don't have to be the same as the endpoints that were

2   studied in the original trials. We have a lot of

3   situations where we're pooling studies that weren't

4   even outcome studies and take drawing outcome data

5   from them to find out how to do a non-inferiority

6   study because no one's willing to do a placebo

7   anymore. That's okay.

8   What Norm says is usually, we're very

9   fastidious about going to a second endpoint if you

10   haven't left room. You've used up your alpha as

11   various people on this committee have said. I don't

12   think it -- I'm not sure how much that matters here.

13   The results are a little worse if you look at the

14   quadruple endpoint than the triple endpoint, but that

15   doesn't affect the calculation of M1 at all. It does

16   affect whether you've made M2.

17   One of the things we like to say is that M2,

18   you're supposed to use some intelligent judgment.

19   Maybe there's some more flexibility. But it is worth

20   mentioning it doesn't really affect the conclusions

21   about M1.

22   DR. HARRINGTON: No, you're moving to

1 whether it's a 66 percent preservation or 75 percent

2 preservation.

3   DR. TEMPLE: Yes, I'm not dismissing it and

4 having an infinite number of shots at the goal creates

5 its own problems. We're very conscious of that.

6   DR. HARRINGTON: Bob O'Neill.

7   DR. O'NEILL: Yes. The sort of general

8 approach in clinical trials has been the composite.

9 I'll throw more into the composite if it's a

10 superiority trial because I'll have more numerator

11 events and I'll increase my power as long as most of

12 them a priori are likely to be impacted by the

13 treatment. That's sort of been the philosophy.

14   But that works against you in non-

15 inferiority trials if, in fact, you willy-nilly throw

16 in endpoints that are neutral. And I made that point

17 a little earlier. And that's what the issue is.

18 TRANSCEND sort of suggests that might be the issue.

19 And Sid brought up the point if you look at the

20 Kaplan-Meier curves over the entire TRANSCEND study,

21 you have an   non-proportionality going on. So

22 you have another complexity thrown in here because

1 you're trying to reduce the treatment effect to a

2 single hazard ratio that reflects the treatment effect

3 over a four- or five-year period when, in fact, it may

4 not be constant and the action may be early or it may

5 be late.

6   So the extent to, which the composite

7 endpoints either expresses that more severely or

8 neutralizes that is an important issue to talk about.

9 So I think that's where you need a lot of help with

10 the epidemiology and everything else. And

11 unfortunately, HOPE was the only study that was

12 available at the time, and it seemed liked a

13 commonsense thing to do that looked they didn't have

14 any difference in their endpoints, three endpoints or

15 four. And so let's throw more numerator endpoints

16 into the game, and that'll help us in non-inferiority.

17 But we're having this conversation because of that

18 issue.

19   So I'm not trying to muddy the water, but

20 I'm saying that's what makes this kind of situation in

21 non-inferiority trials very difficult to interpret.

22   DR. HARRINGTON: Emil and then we'll go -- I

 1   think Dr. Yusuf would like to say something.

 2   DR. PAGANINI: Just a quick thing. Do you

 3   think that the fourth element of congestive heart

 4   failure hospitalization reflects a changing pattern in

 5   congestive heart failure treatment and hospitalization

 6   over the eight years and maybe that moving target is

 7   the one that sort of ruined the comparison? Because

 8   you have a fixed set of data up through '01 or '02 and

 9   then you have a difference in treatment of congestive

10   failure over the next eight years that may have moved

11   that portion of that fourth target a bit to then move

12   that entire target off.

13   Whereas, if you used the secondary

14   endpoints, which were the same endpoints as the

15   primary endpoints minus the congestive heart failure,

16   I have less of a problem with a secondary analysis of

17   the same elements that were in the primary analysis

18   minus a moving target that may have muddied the water.

19   DR. HARRINGTON: So you're in part getting

20   to the last question -- and I'll get to you next,

21   Dr. Yusuf -- this evolving treatment of high-risk

22   patients because one of the things they showed that's

1 most striking is the increasing use of beta-blockers.

2 Now, we've not seen it, what beta-blocker use by

3 ejection fraction is, et cetera. But over that period

4 of time, the use of beta-blockers became more standard

5 in heart failure patients. So certainly, a

6 hypothesis, Emil.

7   Dr. Yusuf. Oh, I'm sorry. Let's go to Bob

8 and then --

9   DR. TEMPLE: That last is a very important

10 point. People have asked us how to get a new ACE

11 inhibitor for heart failure into the marketplace.

12 We've basically said we don't know how you can do

13 that. Since you did those trials, everybody's on a

14 beta-blocker, everybody's on spironolactone. We don't

15 know what the effect of --

16   DR. HARRINGTON: And they're no longer in

17 DIGE, which might not have been helping.

18   DR. TEMPLE: So here, that may well be the

19 explanation of why that one didn't show up as well.

20   DR. HARRINGTON: And the beta-blocker

21 differences are substantial as we go through the

22 trials.

1   DR. TEMPLE: I want to make one other point.

2   Even if you -- suppose they'd won because they'd did

3   bang up on it because they really showed something

4   terrific on heart failure, but the other stuff all

5   went in an adverse direction, that would not make it a

6   very attractive substitute. It would tell you it does

7   something maybe, but it wouldn't make it seem like it

8   replaces ramipril. So it's okay to use combined

9   endpoints because otherwise you probably can't do it.

10   But we do look at the components and get nervous or

11   excited, depending on.

12   DR. HARRINGTON: Depending upon the

13   directionality.

14   Dr. Yusuf.

15   DR. YUSUF: I think Bob Temple made the

16   point I wanted to make, that irrespective of, which

17   endpoint you look at, whether it's the one with heart

18   failure or without heart failure, we make M1. So

19   really, the issue around M2 is then what percent of

20   the benefits do you preserve. In our calculations,

21   which is it's a calculation when the trial is

22   finished, it's not related to the margin is 66 percent

1   for the quadruple and 75 percent for the triple.

2   I actually agree with -- I'm going to speak

3   out of both sides of my mouth, which is not

4   infrequent. On one hand, I do agree with the

5   statisticians. You do have to pay some attention to

6   the fact that our primary endpoint was a quadruple and

7   what happened to that in interpreting the second one,

8   you have to. At least informally, you should

9   recognize that. But the second part of it is the

10 point that Bob O'Neill raised, it bothered me a lot

11 that I didn't see anything on heart failure on the

12 first time to first (unclear) in TRANSCEND. It really

13 did, Bob.

14   There were many explanations, and I explored

15 those explanations in the database. The first

16 explanation was could we be doing something to the

17 control group that masked a potential benefit. So we

18 looked at imbalances in post-randomization treatment.

19 And there is a marked difference in diuretic use.

20 It's about 33 percent in the telmisartan group. It's

21 about 40-odd percent in the control group.

22   Now, obviously, if you play games with

1 numbers and said cook your whatever endpoint including

2 heart failure plus starting new diuretic, obviously,

3 you get a hugely significant difference. You'll turn

4 around to me and say, well, preventing diuretic use

5 isn't big. But on the other hand, it gives you an

6 explanation on that.

7   The second I asked myself was did we have

8 the play of chance going against us. And that I

9 believe is a possibility. And if you can put up that

10 slide on the multiple events, the CE-34. And when you

11 look at that, that is the imbalances. Beta-blockers,

12 there was an imbalance, but that's not huge. But the

13 diuretic probably may have mattered, the one I told

14 you.

15   This is what told me that we probably had a

16 bad break, and you can have a bad break even when you

17 have a trial with 2, 300 endpoints for a given size.

18 Because the first endpoint, there's little difference

19 of anything slightly the wrong way. But when you look

20 at multiple events, it's 175 versus 210. And you can

21 do a simple arithmetic there, 175 take away 23 is 52.

22 So second events are 52 in the telmisartan group. And

1   in the placebo group, you can do the same thing. It's

2   98.

3   So there's a big effect in preventing

4   multiple events. And as David said earlier, we have

5   to look at everything. So when you look at heart

6   failure on everything, there actually is the expected

7   difference. And therefore, I believe it is not

8   unreasonable to both look at the quadruple endpoint

9   and the primary endpoint and honestly, Bob -- and this

10 is Bob O'Neill -- we had no intention to play the game

11 let's throw in endpoints that are insensitive so it's

12 easier to show non-inferiority. We certainly did not

13 do that. It was never our intention, and even now I

14 would say I think it was a sensible decision. Had we

15 had enough power, we would have gone with the 3-fold

16 endpoint and reversed it and put the heart failure as

17 the secondary endpoint. The issue was power. The

18 issue was feasibility.

19   So coming back to this, I think the

20 committee's fair in looking at both endpoints. I

21 think the committee's fair in giving greater clinical

22 weightage to the triple endpoint. I think, though, M1

1   is satisfied by both and there is an explanation why

2   heart failure on the first endpoint wasn't changed.

3   But heart failure on the second endpoint was highly

4   changed in TRANSCEND.

5   DR. HARRINGTON: Thank you.

6   If you could go back to the questions,

7   Elaine.

8   I think we've had a good discussion, Norm,

9   about Question 2 and about the HOPE trial. I think

10 we've talked about the issue of the single reference

11 study. We've talked about the endpoints. We've

12 talked about early termination. We've had some

13 discussion about evolving treatment.

14   So let's move to Question 3, which gets into

15 this issue that Bob O'Neill brought up this morning

16 that more data does become available. And when you're

17 doing a non-inferiority study, you need to take that

18 into consideration. And so the question is, are

19 EUROPA and PEACE with two different ACE inhibitors

20 than ramipril and different from one another relevant.

21 And, if so, given the results of EUROPA and PEACE,

22 which you have in your handout with the hazard ratios,

1 how confident are you in the constancy assumption and

2 what discount on the expected effect of ramipril is

3 appropriate?

4   So who wants to kick us off? Sanjay, do you

5 want to start to address the question? So you can see

6 trials spanning over seven years here, 1993 to 2000.

7   DR. KAUL: Right. I think pooling the data

8 runs counter to the spirit of the ICH guidance that

9 states that the margin should be specified a priori

10 but is consistent with Salim's exhortation to us that

11 we should pay attention to the continuum of evidence.

12   So I have problems reconciling the two. I

13 would have just stuck with HOPE as my reference

14 population to draw the non-inferiority margin. As a

15 general rule, the assumptions underlying

16 non-inferiority are problematic because they're not

17 verifiable, especially the constancy assumption and

18 assay sensitivity.

19   Whatever little data that I saw addressing

20 constancy assumption seemed to suggest that there is

21 constancy in terms of the hazard ratio. But I'm not

22 confident that's everything that the constancy

1   assumption asks us to capture. So because I'm not

2   confident in the constancy assumption, ergo, I'm not

3   quite sure what discount to apply. So there's

4   uncertainty with regards to that.

5   So I can do some sensitivity analysis and

6   see whether it meets the criteria based on different

7   degrees of discounting, and I think that would be

8   acceptable. And I'm going to stop there.

9   DR. HARRINGTON: Go ahead, Norm.

10   DR. STOCKBRIDGE: This has come up a couple

11 of times, and I'd like to say I think there are two

12 very distinct purposes to advising people to get

13 the -- to pre-specify and work out what the

14 non-inferiority margin is. One purpose is the same as

15 it is for any clinical trial. It's to crystallize

16 what the hypothesis being tested is. But there's also

17 this fungibility to the concept of what constitutes

18 non-inferiority here. There's a great deal of

19 discretion involved in how you do this so that if

20 everything you're ever going to know is known before

21 the trial starts, it makes sense to have as much of

22 that discussion before the trial starts.

 1   But this is unlike a difference finding

 2   trial in that it's entirely possible to have

 3   additional information come available on the

 4   effectiveness of the control agent. And just because

 5   you had a prospective plan to think about that doesn't

 6   mean that you can't or, in fact, shouldn't reconsider

 7   it in light of additional information that comes

 8   available while you are collecting your data.

 9   DR. KAUL: If I may respond to that, I see

10   the value of meta-analysis in explaining away

11   inconsistencies in treatment effect. I know that it

12   is seldom used for this intended purpose. This is

13   what it was originally intended for. It is used to

14   combine data that don't meet the endpoint in the hopes

15   of increasing power and therefore meeting whatever

16   specified endpoint is. I like to use these

17   meta-analysis to explain away the differences, and

18   that's where I see its value. I don't see it valuable

19   to post hoc derive these original endpoints were

20   different, the primary endpoints were different. They

21   were different agents. You're assuming that there's a

22   class effect and so on and so forth.

 1   So that's my fundamental issue with pooling

 2   data to be able to address variances across treatment

 3   effects.

 4   DR. STOCKBRIDGE: Okay. It's perfectly

 5   reasonable to say I don't think you should even pool

 6   these things because they're not coming from the same

 7   product. If that's the way you feel, it'd be good to

 8   have everybody around the table say I don't think one

 9   ACE inhibitor is like another, and then we'll be done

10   with the whole issue of pooling things in classes

11   because there isn't anything that looks as much alike

12   as two ACE inhibitors.

13   But the other aspect of what you said had to

14   do with whether you should incorporate any information

15   you had about anything that took place after you'd

16   formed your hypothesis. And I would assert that if

17   we'd had two more HOPEs, HOPE-II and HOPE-III, that

18   came along, same drug, similar populations, that had,

19   I don't know, shown a bigger effect than HOPE, I would

20   have expected to have all incorporated that and

21   adjusted our thinking about the interpretation of this

22   trial.

 1   It's an entirely a different issue whether

 2   you particularly think these two other trials ought to

 3   be put together.

 4   DR. HARRINGTON: Mori.

 5   DR. KRANTZ: I agree with Norm. I think on

 6   the one hand I respect what Sanjay is saying about a

 7   priori. It's really important to delineate what you

 8   want to do and what you intend to do. But it's sort

 9   of hard to ignore the data and just sort of the issue

10   of heterogeneity within the ACE inhibitor class, I

11   really think it's very different than beta-blockers.

12   My take is if you look at Peles' article,

13   retrospective registry from Canada, perindopril and

14   ramipril were the two best in terms of maintaining a

15   low mortality. So I think those ACE inhibitors and I

16   think even trandolapril were chosen because of tissue

17   lividity, long half-life and this expected benefit for

18   cardio protection. So I think you really can't sort

19   of say they're so different from that regard.

20   DR. HARRINGTON: It's part of the challenge

21   here, isn't it, Norm, when you look at the -- and we

22   had said it earlier and you repeated it that if these

1 were HOPE-I, II and III and the point estimates were

2 moving, that might bother you more. In this

3 particular case, we've got three different drugs.

4   If you go back and look at the slide that

5 Dr. Yusuf showed, in fact, there's a remarkable

6 consistency in the ACE inhibitor data across different

7 populations, LV dysfunction, post-MI, et cetera. The

8 outlier is really PEACE in all of this. It seems that

9 the estimate of effect is somewhere in the .79 to the

10 .85 range for all the trials, and then PEACE is .9

11 something.

12   So how do you reconcile that, Norm? It

13 strikes me that the drug might just -- it's either a

14 play of chance. It's about the fifteenth ACE

15 inhibitor trial or tenth ACE inhibitor trial, and

16 maybe it's just the outlier. On the other hand, maybe

17 there's something really different about the drug.

18   DR. STOCKBRIDGE: Look, I'm as incapable as

19 anybody of trying to tell you why PEACE looks as

20 different from the other two as it does. I will point

21 out that we've certainly seen and considered a

22 cross-ACE basis for comparison in previous trial save

1   AIRE and TRACE were all pooled to define the margin

2   for -- is it Valiant? It was for Valiant.

3   No one seemed to be particularly troubled by

4   the fact those were three different ACE inhibitors

5   then. We were a little bit troubled by the sponsor

6   having picked the one they did for the positive

7   control in that comparison.

8   DR. HARRINGTON: Dr. Pfeffer and then

9   Dr. Fox.

10   DR. PFEFFER: As the co-chair of PEACE, I

11 feel I should add a little bit to that.

12   DR. HARRINGTON: I didn't mean to call you

13 an outlier, Marc.

14   DR. PFEFFER: Outlier is a good term. It's

15 a nice book now, too.

16   But a clinical trial is like your child, so

17 I'm speaking of one of my children here. But before I

18 do that, I'll give an anecdote that goes to Dr. U and

19 Dr. Zhang's very nice review, and everyone said if it

20 wasn't for PEACE, it would be easy. But they also

21 used words like fail and wins, which I have to say the

22 night before I presented Valiant, my son came home

 1 college and he had just taken statistics. So he's

 2 right on top of his game. He took college statistics.

 3 And I said, "Mike, come here. I want to show you

 4 something."

 5   I showed him the slide, and the three

 6 Kaplan-Meiers were superimposable. And I said, "This

 7 is what I was doing for the five years."

 8   And he said, "So, Dad, you wasted five

 9 years."

10   [Laughter.]

11   DR. PFEFFER: Well, it's not so simple. And

12 this isn't so simple. Now, PEACE is one of my

13 children. I'd have to say I think it is the outlier,

14 and I think we wanted to do 14,000 patients.

15 Everything is a compromise. We weren't able to. HOPE

16 had come out. It was harder to keep people on

17 medications. We ended up with not the same size. We

18 made a new composite. And when it was over, when we

19 broke the code, it wasn't what we thought it was.

20   So we started to probe our data. I mean,

21 that's what you do. First, you say it's neutral. You

22 don't say it's failed. And then you say what did we

1　learn from this.　And we found that our absolute event

2　rate was lower, so therefore, wow, here's a

3　hypothesis. Now we've gotten down to the level that

4　when Dave wakes up in the middle of the night, leave

5　him alone.　Go back to sleep, Dave.

6　　　　　　But so we probed.　And then the other

7　studies, we told them we think it's because we have a

8　lower event rate group.　And lo and behold, the EUROPA

9　people who had an ever lower event rate than HOPE

10　start slicing and dicing their data and saying no,

11　every time we go down, it's still there.　The relative

12　risk is still there.　HOPE, slice, relative risk is

13　still there.　So then it makes us feel well, what is

14　wrong with us.　Is it the drug?　I don't think so.　We

15　spent the government's money.　This is NHLBI, and we

16　didn't want to use a drug that wasn't studied and we

17　picked trandolapril.　It was used once a day in trace,

18　so we don't think it's the drug.

19　　　　　　However, people didn't take it as much.　And

20　that's -- we didn't get to the full dose as much and

21　we didn't have as many people taking it.　So I'm

22　making excuses for my child.　I do think it is an

1   outlier, and I think when people think of M1 -- and

2   I've learned a lot today of this M1 concept. I want

3   to throw something in. What I think M1 is, M1 is what

4   the clinicians do today because of all the knowledge

5   that they have. No one leaves your cath lab tomorrow,

6   no one leaves our intermediate care tomorrow, no one

7   leaves our clinic tomorrow with known coronary disease

8   without trying an ACE inhibitor. And it's because we

9   believe the M1 today is as good as it was 10 years

10 ago.

11   DR. HARRINGTON: Marc, just before you sit

12 down, could you just -- I think I heard you this

13 morning in PEACE when you said 50 percent

14 discontinuation of the study drug. Was that -- or did

15 I mishear that?

16   DR. PFEFFER: I don't have the numbers in

17 front of me. But at two years we published in our

18 manuscript, and it wasn't something we were proud of.

19 This was anymore and I'll have trouble with my

20 children here. It was we'd like it to be better, but

21 at two years it wasn't what we thought it would be.

22   DR. HARRINGTON: So there's at least a

1   potential explanation for it being an outlier?

2   DR. PFEFFER: The big explanation we gave

3   was the low event rate. As a matter of fact, in our

4   manuscript, we talk about the fact that at the

5   annualized event rate for males and females age

6   adjusted in our population was about that of the

7   national population and everyone was selected for

8   coronary disease. So then we were scratching our

9   heads, how can you make people better? That was an

10 explanation, which was blown away by the EUROPA

11 analysis finding a lower and lower rate risk.

12   I don't have a number, but I'd have to tell

13 you, I just -- we would have liked it to have been

14 better.

15   DR. HARRINGTON: Okay. Let's finish up on

16 the question here.

17   DR. YUSUF: I have the numbers.

18   DR. HARRINGTON: Okay. If you could just

19 give them to us, so we can continue to go through the

20 questions.

21   DR. YUSUF: In HOPE, at two years, 85

22 percent were on the study drug. In PEACE, 78 percent.

1 At target dose at the end of the study, 75 percent in

2 HOPE and 68 percent in PEACE. So it's not terrible,

3 but it's significantly lower.

4   One other little point can I just say, if

5 you pooled EUROPA and HOPE, there's no change in the

6 non-inferiority margin.

7   DR. HARRINGTON: In fact, I think the FDA

8 showed us that this morning, correct, yes.

9   DR. YUSUF: If you pool all the trials of

10 ACE inhibitors, including the LV dysfunction thing,

11 then there's no change in the margin. So it's only if

12 you pool EUROPA, PEACE and HOPE together there is a

13 change, but it isn't a huge change. There is some

14 change.

15   DR. HARRINGTON: I think the FDA pointed

16 that out as well, if I recall.

17   As we look at 3.2, maybe I could ask our

18 biostatistician friends on the panel, is this

19 something we should spend a lot of time talking about,

20 Ralph or David, if we're trying to get the overall

21 effect size of ACE inhibitors whether or not we use

22 the fixed effect or the random effect modeling of the

 1   meta-analyses. Dr. Yusuf addressed some of that this

 2   morning, but I'd like to hear from the two of you and

 3   then we'll go to you, Jonathan.

 4   DR. D'AGOSTINO: I agree with the comments

 5   that were made this morning. We have a small number

 6   of trials. They're completely unequal in terms of

 7   sample size. I think what was done by the sponsor,

 8   using just the HOPE, that's what they had at that time

 9   was fine. Adding new information, I don't think would

10   have helped. If you did a meta-analysis, forget what

11   we have on the table here, but in general if you're

12   dealing with a small number of studies and you're

13   trying to work out a margin and you run to a random

14   effects model, you start adding a lot of assumptions.

15   That there's equal variability or variability that you

16   should be taking into account and you get some

17   anomalies like we saw this morning.

18   I'm much more comfortable in terms of

19   getting at a margin with a small number of studies to

20   use fixed effects. I am much trouble trying to say is

21   this study appropriate in the meta-analysis that I

22   have with this random effects modeling and so forth.

1   And I think some of the literature that we've seen

2   recently in terms of picking up potential problems

3   with drugs causing some tremendously bad side effects

4   have a lot to do with the fact of this random effects

5   modeling versus fixed effects modeling discussion. I

6   think it's much safer in this setting to stay with the

7   fixed effects.

8   DR. HARRINGTON: David, do you have a

9   comment on that?

10   DR. DeMETS: Well, to keep it short, I agree

11   with that for all the reasons that have been said.

12   I'm not a random effects guy.

13   DR. HARRINGTON: Bob.

14   DR. O'NEILL: I don't think this is a place

15   for that discussion, but I must say that the

16   non-inferiority guidance is going to put this idea out

17   there. And it says you don't get away -- it sort of

18   gets at the heart of when you don't have one -- when

19   you only have a single study, take your choice. You

20   either impute a variability that you have not seen yet

21   because we know that there is study-to-study

22   variability. We can show you from many different

1 areas. So there's that concept.

2   Now, whether you want to call it fixed

3 effects or random effects, you can call it what you

4 want. But I think Sanjay was talking about

5 meta-analyses also is useful for explaining

6 heterogeneity, and that's what this is about. So it's

7 essentially how do you take and pay a price for

8 heterogeneity given some of it you haven't seen

9 because you only have one study and given in other

10 studies where there is a fair amount of heterogeneity.

11   And this issue goes to when you got a lot of

12 studies and when you have a few studies. It was a big

13 ticket item in the Avandia meta-analysis of 43 studies

14 and trying to explain heterogeneity. It's a big deal

15 in the ADHD drugs and suicidality. It's a big deal in

16 safety meta-analyses. But it's not worth talking

17 about here.

18   I think the focus on HOPE in a single study

19 and that's what the margin was based upon, that's sort

20 of I wouldn't expand that conversation. But this is

21 something that shouldn't be blown off. It will come

22 back again at another time because it's in our

1   guidance.

2   DR. HARRINGTON: Sanjay, hold on one second

3   because Jonathan's been waiting, then I'll come to

4   you.

5   DR. FOX: Thanks very much, Bob. I just

6   wanted to maybe interject a comment that was

7   stimulated by something I think Dr. Stockbridge said,

8   which was around the advisability or at least the

9   potential benefits of looking at additional

10   information as it accrues since starting a trial. So

11   clearly, the sponsor had only the one study to go on

12   at the beginning. But then these other studies came

13   in in the interim, and the FDA I think appropriately

14   said well, let's take a look at these other data

15   within the class and see if they provide any greater

16   illumination to some of the issues we've been

17   struggling with today.

18   Just in case anybody might get the wrong

19   impression however, I think that while I speak for

20   myself just as a personal opinion, I think the agency

21   is correct in requiring sponsors of potentially

22   competing products that do their own trial rather than

1   if one sponsor with a product does a successful trial,

2   that they don't just declare class effect without any

3   other considerations. If you're the sponsor with a

4   successful trial, you cry foul. If you're numbers

5   two, three and four, you say yippee.

6   But I think scientifically, there are

7   potentially enough important differences between

8   molecules in a class that it's fundamentally important

9   to study each one on its merits however challenging

10 that might be as today's example provides. So I just

11 wanted to add some clarity around that.

12   DR. HARRINGTON: Thank you.

13   Sanjay.

14   DR. KAUL: I was going to have an offline

15 conversation with Dr. O'Neill regarding the choice of

16 the model.

17   DR. HARRINGTON: Okay. Just in the way of

18 procedure, let's do Question 4. And this really gets

19 at Bob's question about M1 and M2 where we said we'd

20 put this discussion and then we'll have Question 5 and

21 then the voting question. We're going to take a break

22 after four because we have to enter another question

1   into the voting system. So we'll take about 10

2   minutes. So everybody that's looking tired, try to

3   perk up for one more question here and help the agency

4   think through this one.

5   "What should the non-inferiority margin be?"

6   Sanjay, you've already stated that you

7   believe that the more conservative estimate provided

8   by the agency analyses is more comfortable to you. Is

9   that a accurate reflection of your remarks?

10   DR. KAUL: Actually, if I were to accept

11   statistical reasoning as the most important way to

12   estimate margin. I personally believe it should be

13   purely a clinical judgment exercise, and then you need

14   to demonstrate that it is statistically conservative.

15   That is my personal belief.

16   So to answer this question what should the

17   non-inferiority margin be, whatever maximum loss in

18   efficacy you're willing to accept for the ancillary

19   benefits. What are the benefits? Well, there is a

20   cough benefit, an angioedema benefit, cost, not

21   really, ramipril is general. Convenient, not really,

22   once daily. So it all boils down to what are you

1   willing to accept. What degree of inferiority are you

2   willing to accept?

3   That is where I was trying to lead the

4   discussion to. What is a clinically meaningful

5   benefit? And so I am not going to share with you what

6   I think is a clinically meaningful benefit and

7   therefore what the margin should be. Maybe we can

8   address that later. But that's where I think my

9   answer is.

10   DR. HARRINGTON: No, this is where we should

11 be now.

12   DR. KAUL: Oh, it should be now?

13   DR. HARRINGTON: Because that's what Norm

14 and Bob want to know is what are people sitting around

15 the table think the margin ought to be.

16   DR. KAUL: Well, if you were to ask me that,

17 I would say it should be less than what the delta is

18 used for is superiority trial. So I'm perfectly

19 comfortable with a margin of 10 to 15 percent given

20 the ancillary advantages of the ACE-induced cough and

21 the angioedema.

22   DR. HARRINGTON: You mean excluding a 10 or

 1   15 percent?

 2   DR. KAUL: 10 to 15 percent, right.

 3   DR. HARRINGTON: Bob, you looked like you

 4   were ready to jump over the table.

 5   DR. TEMPLE: You wouldn't want to believe

 6   that we set a minimum effect in an outcome trial to

 7   declare victory. We declare victory when you win. If

 8   you reduce mortality by 5 percent, we say that's not

 9   as good as 20 percent, but on the whole, alive is

10   better than dead. So we don't have a fixed value. We

11   talk about that here because you're trying to

12   substitute for a drug that has a known value.

13   But I want to go back to your first thing.

14   You can't set your clinical margin until you know how

15   big the effect is. That's what people used to do.

16   It's what we used to do. We'd set a margin for

17   anti-infective drugs and even for cancer drugs. We'd

18   say well, as long as the difference is less than

19   10 percent, that's not bad. But we didn't even know

20   that the drug we were saying okay to had any effect at

21   all. That's why you have to figure out M1 first. You

22   have to figure out what difference you've ruled out,

1 and then you can talk about how much of the control

2 drug you want to retain. The logic breaks down if you

3 don't do that. You can't say it.

4   Unless I'm positive that the drug had an

5 effect, how can I say what percentage of anything I'm

6 keeping? So this is all explained in enormous in our

7 non-inferiority guidance. But you really have to

8 figure out what the trial is capable of showing in

9 terms of retained effect. And we treat it

10 conservatively so our advocacy for 16 percent is

11 smaller than theirs because we take the lower bound of

12 the confidence interval instead of a point estimate.

13 You could debate that. It is conservative. We know

14 it is.

15   But really only after you do that can you

16 then go and say well, okay, now how much of it do I

17 have to retain? The logic breaks down unless you do

18 that.

19   DR. HARRINGTON: Go ahead, Ralph.

20   DR. D'AGOSTINO: Again, I think the FDA

21 argument; that is, the presentation that was made by

22 the FDA people is very sensible. You look at the one

1   study, look at the confidence interval, get the lower

2   bound and then talk about some kind of discounting.

3   And so their 1.08 from a statistics point of view, I

4   agree that it's not clinical, but from a statistics

5   point of view, it has a logic to it. It's

6   conservative. And unless I hear an argument that it's

7   not clinically meaningful, I don't know where to move

8   away from it.

9   I do think that the material or the

10   computations that were done by the sponsor are

11   computations, which we used to discuss a number of

12   years ago and we sort of moved away from them because

13   of the fact that there was only one study here. If we

14   had lots of studies, then your variations starts

15   decreasing. But I think theirs was a little bit more

16   generous than I think we should live with.

17   DR. HARRINGTON: And this, Bob O'Neill, I

18   think was your point a few minutes ago that somehow

19   you have to take into consideration the variability,

20   that whether you have observed variability because you

21   have multiple studies that you've measured or you have

22   some estimate of the variability if you only have a

 1   single study.

 2   DR. O'NEILL: Yes, that and more. The point

 3   that Bob Temple was trying to make is that you can't

 4   begin to have a clinical judgment on this issue unless

 5   you can show me the money. And what that means is

 6   show me the evidence for what the effect size is of

 7   the active control. That's a very empirical database

 8   only issue.

 9   What we're talking about here is you've got

10   two choices in that matter. You've got a single

11   study. You either put your money on the point

12   estimate. Most people say that's much too liberal.

13   Put your money on the lower bound of that, which

14   essentially is consistent with at this point in time

15   the 95 percent confidence interval is a coverage

16   concept. It says the true value of the effect size

17   could be anywhere in there, lower or higher or in the

18   middle.

19   Right now, I'm going with the conservative

20   choice, and it's going to be the lower bound. And

21   that's your best empirical shot. Now, let's have the

22   conversation about how much of that you want to

1   preserve. So that's the logic of what's going on

2   right here. And there's some confusion with I can

3   throw any percent out there that I want because

4   clinically. But yes, that hides -- commit to me on

5   what the delta is first before you throw your percent

6   out there of what you want to preserve.

7   So I think that's what Bob is saying.

8   Before you tell me -- and because that's where the

9   flexibility is. And I think what we're talking about

10   here is this margin that's been set flexible in the

11   sense that it's a clinical margin and you've already

12   passed and this data supports the fact that the drug's

13   effective. It may not preserve 50 to 60 percent, but

14   you're pretty convinced that it's effective.

15   I think those are the two issues here

16   because these non-inferiority trials as we've tried to

17   say in the guidance are a substitute for a superiority

18   trial. And they're not only a substitute for a

19   superiority trial where the null hypothesis is reject

20   and show me that there is some difference. They're

21   also trying to achieve another thing. And the other

22   thing is show that you've preserved a certain

1 percentage. But you cannot be silent on what that

2 effect size is. So that's why I'm trying to force

3 the -- it can't be a lead with the clinical argument

4 issue. It has to lead with the empirical evidence

5 first.

6   DR. HARRINGTON: In which this case, then

7 the discussion largely becomes around what do you make

8 of HOPE and where -- what do you want to say that

9 you're willing to drift away from that once you've

10 established what that is and whether or not you want

11 to discount it with PEACE and EUROPA or you want to

12 leave it as its estimate with its associated

13 confidence interval.

14   DR. O'NEILL: Right.

15   DR. HARRINGTON: Okay. Bob and then Sid.

16   DR. TEMPLE: It turns out when you pool

17 data, you narrow the confidence interval. So in this

18 case, you lower the point estimate when you pool the

19 three, but you narrow the confidence interval. So the

20 lower bound of the confidence interval is not that

21 different. And it comes out sort of the same.

22   In a more non-specific way, however, because

1 pooling isn't the only approach, you could be

2 non-specifically nervous and say oh, I don't think

3 it's really -- 16 percent seems too big now. I'm

4 going to shrink it in some non-specific way. That's

5 the proper use of the term discounting. We don't like

6 the -- it's too ill-defined. Anybody can discount by

7 whatever he wants, but nonetheless, we do that

8 sometimes.

9   But in this case, whether you pool them or

10 take just HOPE, it turns out the same, the same lower

11 bound.

12   DR. HARRINGTON: Like I said, we saw that

13 this morning.

14   Go ahead, Sid.

15   DR. WOLF: When I raised before the issue

16 that we have to look at the placebo-control trial,

17 TRANSCEND, when we think about the inferiority margin,

18 just for a second to just go the step beyond that. In

19 HOPE itself, there was a 22 percent reduction and

20 fairly narrow confidence intervals, .7 to .86. In the

21 3-component look at TRANSCEND as was pointed out by

22 Salim, it's 13 percent reduction, but the confidence

1   intervals are very close. It's .76 to 1.00. So just

2   looking at those two studies, one is concerned about

3   whether one wants to calling it waking up in the

4   morning or whatever, recommending the approval of this

5   drug is essentially saying to people you can use a

6   drug that didn't do anywhere near as well in a

7   randomized placebo-controlled trial as HOPE the older

8   drug, the less expensive drug. And morphing over to

9   the inferiority margin, this kind of uncertainty --

10 and I realize that we're looking backwards a little

11 bit because the randomized placebo-controlled trial

12 TRANSCEND was after HOPE and after this other one was

13 begun -- but there's a level of discomfort about

14 making a decision to approve something that there's a

15 reasonable chance that it's not as good as something

16 that's already on the market.

17   And I think that just looking at these two

18 vastly different results from the two placebo-control

19 trials on the drug and then combining that with FDA's

20 cautious approach and that's where I would answer it

21 at .08 for the inferiority margin sort of justifies

22 the caution. The caution is not just abstractly

1 looked at in the non-inferiority study. You have

2 these other two studies that really give me a lot of

3 pause for concern. So very conservative margin is I

4 think the public health safest one.

5   DR. HARRINGTON: Ralph?

6   DR. D'AGOSTINO: I don't disagree with

7 anything that was just said in terms of what the

8 Gestalt would be. And when I look at all the

9 evidence, the comment I made and I think that was made

10 here by others is that what do you do with this

11 non-inferiority. And I don't think you necessarily

12 have to bring in, though it's where the clinical

13 judgment starts coming in.

14   We have this 1.08 margin that came up from

15 this sort of formal discussion. And how does the

16 clinical inform that? And I guess you could say the

17 clinical, which you're suggesting, Sid, is the

18 clinical informing that. I think that there's

19 probably enough just with the 1.08 and the sort of

20 discussion that went around that to live with that

21 number. But I don't know how the added information

22 would sort of change it up and down except saying we

1   were probably right doing the conservative approach.

2   DR. HARRINGTON: Let me go to David, then

3   Sanjay.

4   DR. DeMETS: I wasn't at the meeting. It'll

5   be interesting how the discussion went. But if each

6   party comes in with their non-inferiority margin and

7   he said 1.08 is interesting if there's a logic to

8   that, but we can't do it because the sample size is

9   55,000 or whatever it was.

10   I wish the discussion would have converged

11   and said well, is there a compromise that we can agree

12   to, somewhere between 1.08 and -- 1.13 is probably

13   just a bit too liberal and 1.08 is good, but we can't

14   do it. That apparently didn't happen. I don't know.

15   But 1.1 sounds pretty good to me as a compromise, but

16   we didn't have that conversation, I guess. So we're

17   trying to beat on the point spread after we've played

18   the game, and that's pretty tough.

19   DR. TEMPLE: One of the permissions we give

20   ourselves in the non-inferiority guidance is some

21   flexibility on M2 to make the kinds of judgments David

22   is talking about. In this case, it depends a little

1   on the endpoint because they're pretty close to 1.08

2   on the triple endpoint, which some of you think is

3   better and not that far on the other endpoint. And

4   you could decide -- that's what we're asking you -- is

5   that close enough or is it sufficiently far that

6   you're still a little nervous?

7   But there is some flexibility on that and

8   not to repeat myself over and over too much, you are

9   very sure that it has some effect at least to the

10 extent you believe in HOPE and the other drugs. So

11 then the question is the clinical judgments. Sid's

12 raising a perfectly good issue. Why do you want to

13 switch to something you're not quite sure is as good?

14 Perfectly good question.

15   DR. HARRINGTON: Yes, I think Sid's getting

16 at the essence of the question, which is that we can

17 set the rules and then to get to your question, Bob,

18 about M2, that is the what are you willing to give up.

19 And for something -- if you have something that's

20 pretty darn good, we've established that we believe

21 that ramipril is pretty darn good, how much of that

22 are you willing to sacrifice not for intracranial

1 hemorrhage but not cough intolerance and angioedema,

2 not to trivialize those. We know that they are

3 important, but I think Sid's bringing up the very

4 important what is the public health imperative. You

5 don't want to send the message that one can be used

6 instead of another unless you're pretty darn sure

7 given what the one that's already being used is

8 preventing.

9   DR. TEMPLE: It's worth making two points.

10 People that pointed out -- I'm not in the business,

11 that a lot of people stop their drug because of the

12 cough and other stuff. If that's true, then it

13 doesn't matter that it's not an intracranial

14 hemorrhage. They just stop the drug that could save

15 them.

16   The other thing is worth remembering, we're

17 treating all these things relatively conservatively.

18 We're asking you to rule it out at the lower bound of

19 a 95 percent confidence interval. That is not the

20 only piece of information in there. And we think

21 that's entirely appropriate. We think they should be

22 treated conservatively, but it's worth being mindful

 1   of that.

 2   DR. HARRINGTON: Point well taken.

 3   Okay. You got to keep it brief, Dr. Yusuf.

 4   Then I'll go to Dr. Paganini and Dr. Kaul.

 5   DR. YUSUF: I think I just want to

 6   reemphasize what Bob Temple said just now and before

 7   that, which is the point I was going to make first.

 8   The margin doesn't really matter when the whole thing

 9   is finished. We've finished the trial. You can then

10   calculate whether you meet M1. You can calculate

11   whether you meet M2. It's not so much meet M2. It's

12   what is the estimate of M2.

13   I mean, whichever margin we use, whichever

14   you use, you do meet M1. Then the issue is what

15   proportion of the benefits do you preserve. And for

16   the quadruple endpoint, 66 percent, for the triple

17   endpoint, 75 percent, that's the lower confidence

18   margin.

19   Now, as a clinician, you may say I don't

20   want to take that risk. So if a patient is going to

21   take -- tolerate an ACE inhibitor, then you say I'll

22   start with a proven ACE inhibitor, ramipril. But if

1   it's not tolerated, what do I do? This is a relevant

2   question. Do I just willy-nilly pick out an ARB out

3   of any that's on the market that has no data at a dose

4   that I don't know what it does, that's a decision most

5   of us who are clinicians here face every day.

6   And I think that's a relevant discussion.

7   And I think the point that Bob said, we've got to look

8   at all the data, and the data's not just the first

9   endpoint. Look at the multiple endpoints. Look at

10   the hospitalization data. And that gives you a

11   certain confidence that even in a different

12   population, which is what the ACE intolerant

13   population is, you get a clinically worthwhile effect,

14   about 13 percent. So you'd like -- most of us like

15   the triple endpoint. That shows 13 percent in

16   TRANSCEND. If you look at multiple endpoints, it

17   shows 13 percent. If you look CV hospitalization,

18   it's in that ballpark. So that's the number to go

19   with rather than at this stage discussing the margin.

20   It's what do we have.

21   DR. HARRINGTON: So we're going to get into

22   the various components here.

1   Go ahead, Emil.

2   DR. PAGANINI: Just a quick issue, if, in

3 fact, we do look at a 66 percent or 75 percent, that's

4 a 33 percent or 25 percent loss of efficiency in that

5 population. And you're trading that off for a 13

6 percent improvement in a population that couldn't take

7 the drug. So being a clinician and knowing how

8 clinicians usually think, if that drug is considered

9 to be equivalent to ramipril, then why would I use

10 ramipril when I can use a drug that has less side

11 effects? So what you're doing then is trading off.

12 And as a clinician, what they will do is say I'll use

13 the drug that has less side effects because in those

14 people that are affected by it, they have a 16 percent

15 improvement. However, you're trading off a 33 to 25

16 percent decrease in effectiveness in the three issues

17 that are very important, stroke, MI and et cetera.

18   The trade-off there even as conservative as

19 you are is still a relatively large clinically

20 important decrease in effectiveness.

21   DR. TEMPLE: No, that's 33 percent of the

22 16.

1   DR. PAGANINI: I understand.

2   DR. HARRINGTON: I think that's what's

3   bothering Dr. Wolf. I think that's what's bothering

4   Norm and Dr. Temple as they pose these questions. I

5   think that's exactly. You've summarized nicely, Emil,

6   what I think is troubling people and why we're here.

7   DR. YUSUF: That's not the right --

8   DR. HARRINGTON: Sanjay, go ahead.

9   DR. KAUL: Well, I just wanted to clarify my

10 position. The statistical reasoning of the FDA does

11 not escape me. In fact, my perspective is in complete

12 alignment with the conservative statistical approach

13 that the FDA recommends.

14   But what I am saying is that as a clinician,

15 I cannot completely discount what is a clinically

16 important difference given the advantages. And if I

17 saved 10 percent, it's, what, 1 point -- if you round

18 it to two decimal places, the margin is 1.09 using the

19 50 percent. And mine is pretty close. So I think

20 we're splitting hairs.

21   We have to ultimately come up with something

22 that we converge on. And I don't think we can

1 discount clinical judgment, and I would like to echo

2 what Emil said.

3   DR. HARRINGTON: Okay. Dr. Yusuf, I'm not

4 going to cut you off, but I also want to move ahead.

5 So we're going to take a break at this point, and what

6 I'd like to do is have you come back in about 10

7 minutes. And if you have a final word, I'll let you

8 make it then, so in about 10 minutes. In the

9 meantime, we'll go ahead and write a question, Norm

10 and Bob, for you to review as a Question 6.1.

11   (Whereupon, a recess was taken from 3:39

12 p.m. to 3:53 p.m.)

13   DR. HARRINGTON: If we could get restarted,

14 we have one or two members who are trying to catch

15 planes, et cetera. So I'd like to make sure that

16 everyone can vote.

17   So the first question or the last question,

18 which is non-voting question is one of the issues that

19 we've been going back and forth on all day, most

20 recently Dr. Wolf called our attention to this. And

21 this gets to Dr. Yusuf's comment about bringing in all

22 of the data.

1   So what the FDA is asking us here as a

2 committee is what role do these other observations

3 play in your consideration of the effectiveness of

4 telmisartan for reducing cardiovascular events. And I

5 think you can handle this as a group of questions. I

6 don't think we need to necessarily go individually.

7 But they are categorized as the lack of superiority of

8 the combination. Ralph first brought this up this

9 morning. How do we consider that information?

10   No. 2, the quadruple endpoint versus No. 3,

11 which is the triple endpoint and how does one parse

12 that and what does that make you think of. And

13 Dr. Wolf has most recently addressed that.

14   Then finally, the lack of an effect in

15 PRoFESS, another placebo-control study, which I think

16 we would all admit as Dr. Yusuf described, a much

17 different study. And I think Emil brought this one up

18 also is a placebo-control study with a null effect

19 here.

20   So I'll open it up. How do these other

21 observations play into your interpretation of

22 telmisartan?

 1   Anybody want to - go ahead, Ralph.

 2   DR. D'AGOSTINO: I'll start off again. I

 3   think they're very -- I think what you're doing here

 4   or whoever put these questions together, you're sort

 5   of putting the pieces together. I mean we have this

 6   superiority, and it's just very hard to walk away from

 7   the fact that it wasn't significant and then somehow

 8   or other you ignore it. It's a piece of information.

 9   I think maybe the FDA in its presentation

10   over-interpreted what it was saying in terms of

11   comparing it with just a straight placebo, but it's

12   there. And it's saying that the added ingredient

13   didn't work.

14   The two and three, where was the major

15   endpoint? What was the study endpoint? And again,

16   you can do all kinds of hindsight and say well,

17   congestive heart failure shouldn't have been there.

18   I've argued or I've seen arguments in these advisory

19   committees years ago when I used to participate more

20   often where it was congestive heart failure that was

21   swinging the day. And so you have it going the other

22   way, and you can't ignore what was the proposed

1   primary event. And what do you do after that?

2   So I think that two says to me that if 4-

3   fold was what we were looking at and it didn't work

4   and so what do we make out of that? And I think what

5   you make out of the 3-component, I think you make very

6   little out of it, unfortunately. And then this lack

7   of effect with the placebo-controlled trial, it's

8   sitting there.

9   DR. HARRINGTON: So let me come back to

10   something you said. You said we make very little out

11   of it. The FDA perspective, as I heard it this

12   morning, was you failed on superiority versus placebo

13   in the quadruple comparison, so therefore stop

14   everything else is hypothesis --

15   DR. D'AGOSTINO: I think that's a very

16   formal statistical stand, but it is, in fact -- if you

17   said this is my primary event and here's where my

18   alpha is beginning to -- I'm putting my alpha on this

19   and you don't get statistical significance, in some

20   sense, everything else now is just exploratory and

21   interesting to see. But this idea of putting a full

22   picture together no longer has a justification or an

1   argument to it.

2   DR. HARRINGTON: So you're closer to the FDA

3   perspective on this than you are to the sponsor on

4   this?

5   DR. D'AGOSTINO: Right, I'm definitely

6   closer to the FDA.

7   DR. HARRINGTON: Okay. Dr. Wolf.

8   DR. WOLF: I would add the fifth thing,

9   which I mentioned before even though it's not on their

10 list, which is the HOPE results, 22 percent risk

11 reduction with very narrow confidence intervals. I

12 think that collectively all of these things say wait a

13 minute, be cautious. We are tilting towards not

14 thinking this is as good as ramipril. I think these

15 are all elements that need to be considered. They're

16 data that were part of this whole package we got.

17   DR. HARRINGTON: Yes, I think you've said it

18 well. The way I interpret this, I actually like to

19 look at data in the perspective that Dr. Yusuf has

20 been putting forward, that you're trying to get all

21 the information on the table. Sometimes you're

22 acknowledging that the statistical rigor has perhaps

1   not been met, but you're looking at all the

2   information and trying to be informed.

3   But I think Dr. Wolf brings up the real

4   point that there's this general sense of discomfort I

5   have as to whether or not telmisartan is really as

6   good, truly interchangeable with ramipril.

7   DR. D'AGOSTINO: I think the winds are out

8   of the sail for saying looking at the totality when

9   the statistical procedures and statistical analysis

10   says you didn't make it to begin with. So you can

11   look at all these things and you should, but you can't

12   suddenly salvage something out of a trial that you got

13   hit with at the very beginning.

14   DR. HARRINGTON: So be informed but don't be

15   certain about what you're seeing.

16   Bob.

17   DR. TEMPLE: Just to make one distinction, I

18   don't think there's any evidence here that it is not

19   as good. The question is whether they've shown it's

20   as good. And that's the test we use to --

21   DR. HARRINGTON: Fair enough.

22   DR. TEMPLE: -- determine whether things are

1   approvable. And that's what we're talking about.

2   DR. HARRINGTON: Much better said.

3   Sanjay.

4   DR. KAUL: Can you repeat that, please? I'm

5   sorry.

6   DR. HARRINGTON: Can you repeat your

7   comment, Bob?

8   DR. TEMPLE: The uncertainties we have I

9   think apply to the question of whether it has been

10 shown to be as good because that's our -- or good

11 enough because that's our standard for approval. You

12 don't have direct evidence that it's less good. It

13 might be, but you don't know that. What the question

14 is about is whether they've documented satisfactorily

15 enough that it is as good or good enough within a

16 certain limit or something like that.

17   DR. HARRINGTON: Dr. Fox.

18   DR. FOX: Maybe from a sponsor's

19 perspective, if you had other trials that didn't bear

20 directly on the pivotal but were supportive, were

21 positive studies in and of themselves and were

22 supportive, then that would be a good thing. But if

1 they're not supportive, if they're negative as were

2 some of these kind of brave kind of trials, then maybe

3 the best you can say is they're not supportive. Is

4 that fair?

5   DR. HARRINGTON: I think Norm said this

6 earlier today, if TRANSCEND and PRoFESS where it

7 clearly met the burden of proof as it was set out as

8 originally designed, we would not be here today.

9   DR. FOX: We wouldn't even be here, right.

10   DR. HARRINGTON: Or it's unlikely we would

11 be here today in the spirit of uncertainty.

12   DR. FOX: But I guess I was just looking for

13 some balance there that they're not -- they don't

14 necessarily detract from how you might interpret the

15 pivotal trial, but they're not supportive.

16   DR. TEMPLE: I think people are saying it

17 does detract a little bit because you sort of expected

18 it to win in some of those. Nonetheless, there was no

19 ramipril comparison in those other trials, so you

20 don't really know that it's inferior. There's no

21 information on that. And the point estimate in the

22 comparative trial was on top of each other. So it's

1 really a question of what's been demonstrated I think.

2   DR. FOX: That's kind of maybe a more

3 complicated way of saying if I've done a study and I

4 get a non-significant p-value but I get a numerical

5 trend in a direction I like, then I say well, it

6 trended in the right direction, I like that. If it

7 trended in the wrong direction and I got a

8 non-significant p-value and I'll say pff, we can

9 ignore that one.

10   DR. TEMPLE: Right, and in labeling and

11 stuff, we don't write the drug doesn't work. We write

12 hasn't been shown to work maybe or something like

13 that.

14   DR. HARRINGTON: I don't want to cut off

15 discussion, but I do want to be mindful of getting

16 everybody's votes in. So if, Norm, you have no

17 objection, I'd like to proceed to the voting question?

18   DR. STOCKBRIDGE: Yes.

19   DR. HARRINGTON: Okay. Is everybody okay

20 with that? Perfect.

21   Before we vote, I'm required to read the

22 following statement: We will be using the new

1   electronic voting system for this meeting. Each of

2   you have three voting buttons on your microphone, yes,

3   no and abstain. Once we begin the vote, please press

4   the button that corresponds to your vote. After

5   everyone has completed their vote, the vote will be

6   locked in. The vote will then be displayed on the

7   screen. I will read the vote from the screen into the

8   record. Next, we will go around the room and each

9   individual who voted will state their name and their

10   vote into the record as well as briefly their reasons

11   why they voted as they did.

12   So here are the two questions, Question 6-A

13   was the question that you had received ahead of time.

14   "Should telmisartan be approved to reduce

15   cardiovascular events in patients at high risk for

16   such events?"

17   Again, you'll vote yes or no, and we will

18   ask you to comment on your rationale after the vote.

19   Based on this afternoon's discussion, we have added a

20   second question, Question 6-B for those who voted no.

21   So if you voted yes in 6-A, you will not vote in 6-B.

22   But for those people who vote no, if any, we would ask

 1 the question, "Should telmisartan be approved to

 2 reduce cardiovascular events in patients at high risk

 3 for such events and who cannot tolerate ramipril?"

 4   Again, we'd ask you to vote and comment. Is

 5 there any discussion around the questions or

 6 clarification needed?

 7   Dr. Wolf?

 8   DR. WOLF: The only question is --

 9   DR. HARRINGTON: If you just hit your

10 microphone, you can speak.

11   DR. WOLF: Are we going to have a discussion

12 after 6-A or are we going to have discussions on both

13 of them after both votes? What does the FDA want

14 here?

15   DR. HARRINGTON: Do you have a preference,

16 Norm?

17   DR. STOCKBRIDGE: (Nods no.)

18   DR. HARRINGTON: How about in the spirit of

19 getting everybody's votes in, if it's okay with the

20 panel, we do both votes and then have a discussion?

21   Any objections to that? Okay.

22   Any other points of clarification? Great.

1   I have one more statement then to read. If

2 there is no further discussion on this question, we

3 will now begin the voting. Please press the button on

4 the microphone that corresponds to your vote. Now,

5 remember this is vote 6-A, should telmisartan be

6 approved to reduce cardiovascular events? As Norm

7 pointed out to me to make clear, this is for the broad

8 approval in patients at high risk for such events.

9 Yes, no, abstain, the voting can begin.

10   (Voting)

11   DR. HARRINGTON: So everyone has voted. The

12 vote is now complete and locked in. There are one

13 yes, six no and zero abstain. If we could start with

14 you, Dr. Kaul, say your name into the microphone and

15 how you voted and we'll come back for the rationale.

16   We don't need to do that? So go ahead,

17 Dr. Kaul.

18   DR. KAUL: Sanjay Kaul, I voted yes.

19   DR. PAGANINI: Emil Paganini, I voted no.

20   DR. DeMETS: I voted no. Dave DeMets, I

21 voted no.

22   DR. HARRINGTON: Robert Harrington, no.

1   DR. WOLF: Sid Wolf, no.

2   DR. KRANTZ: Mori Krantz, no.

3   DR. D'AGOSTINO: Ralph D'Agostino, no.

4   DR. HARRINGTON: If we could return to the

5 questions. Now we're voting on 6-B. So everyone

6 except for Dr. Kaul will be able to vote on this one.

7 If you voted no, should telmisartan be approved to

8 reduce cardiovascular events in patients at high risk

9 for such events and who cannot tolerate ramipril. So

10 this is moving from the broader to the narrower

11 indication.

12   Dr. Kaul?

13   DR. KAUL: I have to clarify. I think I

14 misunderstood the question. I thought it was if you

15 voted yes, should it be approved to reduce

16 cardiovascular events in patients at high risk.

17   Is there a remedy for this misunderstanding?

18 I apologize.

19   DR. HARRINGTON: Did you intend to vote no

20 on 6-A?

21   DR. KAUL: That's right.

22   DR. HARRINGTON: Is there a mechanism by

1 which we correct that, Norm?

2   DR. STOCKBRIDGE: Right. I mean, who cares

3 what the vote is?

4   [Laughter.]

5   DR. KAUL: Okay. So next time, make sure

6 you don't invite me to the panel.

7   DR. HARRINGTON: So, Sanjay, I've been told

8 that if you state into the microphone for the record

9 that you'd like to correct your vote to no, that would

10 suffice.

11   DR. KAUL: Okay. Sanjay Kaul. I would like

12 to change, for the matter of record, my vote. It

13 should be no for 6-A.

14   DR. TEMPLE: So now he can vote on 6-B.

15   DR. HARRINGTON: Now you can vote on 6-B.

16   All right. Once again, if there's further

17 discussion, we will now begin the voting process,

18 please press the button on your microphone that

19 corresponds to your vote.

20   (Voting)

21   DR. HARRINGTON: The voting is now complete

22 and locked in. We have five yes, two nos, no

1   abstains. So let's go around the table, but I'm going

2   to take the Chair's prerogative and begin with Dr.

3   DeMets and ask him to identify himself and his vote.

4   DR. DeMETS: Dave DeMets, I voted yes with a

5   lot of issues, but among them are that there is an

6   unmet need of patients not being able to take

7   ramipril. And it was curious to me why the trial

8   TRANSCEND wasn't the featured trial of this whole

9   package since that's the niche that we think it may

10   fit best. On the 6-A question, there was too many

11   close calls. It wasn't overwhelming. I personally

12   wouldn't want to make the switch to these two drugs.

13   But I do appreciate the fact that there is a need, and

14   the evidence is not overwhelming. It's not strong.

15   But it's at least reasonable. So I was willing to go

16   that way.

17   DR. HARRINGTON: Thank you.

18   Dr. Kaul.

19   DR. KAUL: I voted yes because I think it is

20   a reasonable alternative in patients who cannot

21   tolerate ACE inhibitors. And I think in TRANSCEND

22   with the respect to the triple endpoint, the

1   likelihood of reducing events by 10 percent, which in

2   my estimate is a clinically important difference is

3   about 75 percent and that was good enough for me and

4   that's the reason why I voted.

5   DR. HARRINGTON: Dr. Paganini.

6   DR. PAGANINI: Emil Paganini, I voted yes

7   for this specific indication. I voted no on the

8   earlier because I didn't believe that it met the

9   criteria and I was afraid that it would be used as a

10   substitute for a more effective drug in that

11   population. However, in this population, which are

12   resistant or not able to tolerate the ACE inhibition,

13   I think it is certainly better than nothing. And I

14   think they've proven that and, in fact, would be very

15   effective in that subpopulation.

16   DR. HARRINGTON: Robert Harrington, I also

17   voted yes here and for many of the reasons stated,

18   that this was a very difficult discussion today in

19   terms of how certain one can be that the drug is as

20   good as ramipril. And on the other hand, I do think

21   they've met the standard, particularly on the triple

22   endpoint, that it is better than nothing in that group

1   of patients for whom otherwise would be on nothing,

2   that it seems to be a very reasonable choice.

3   DR. WOLF: I voted no on the second one

4   partly because of the sort of marginal effects,

5   positive effects in the TRANSCEND trial but also

6   because looking at concomitant medicines on these

7   people, it isn't just a matter of someone who is

8   intolerant to ACE inhibitors having nothing or this

9   drug. A number of them have not been adequately

10 treated with other drugs known to reduce

11 cardiovascular risk. So I think that the campaign to

12 add some of these other drugs with proven

13 cardiovascular risk lowering abilities would be

14 preferable with marginal unproven.

15   DR. HARRINGTON: And just to help people

16 out, Dr. Wolf, you're referring specifically to what

17 other medications in this population?

18   DR. WOLF: Well, we looked at the secular

19 trend of increased use of lipid-lowering agents and

20 everything, but there still were significant numbers

21 of people who were not on what you and I would call

22 the full regimen, including diuretics and other drugs

1   to reduce cardiovascular risk. So it isn't as though

2   these people have no choices. For the minority or the

3   ones that really are intolerant to ACE inhibitors,

4   their physicians can go to some other drug or

5   combination of drugs as an alternative.

6   DR. HARRINGTON: Bob.

7   DR. TEMPLE: I'm curious. The results of

8   the various trials show that when added to these other

9   drugs, it's true not everybody takes them, but when

10 added to these other drugs, anti-platelet drugs,

11 whatever, these drugs whether it's ramipril or

12 something else have an additional effect. So I

13 totally agree that everybody ought to be on these

14 other drugs, but they should still be on one of these.

15   DR. WOLF: But ramipril does, but I'm not

16 sure that this drug has the effect in people who've

17 been fully treated with other things. I don't think

18 there's any trial that shows that. This one certainly

19 doesn't.

20   DR. TEMPLE: Okay.

21   DR. HARRINGTON: Dr. Krantz.

22   DR. KRANTZ: Mori Krantz. I voted no. I

1 thought it was a really exceptional trial, very well

2 executed. I guess I think we talked a lot about

3 statistical issues. I think the constancy issue was

4 important to me. I really think secular trend in CV

5 mortality have dramatically changed. And I think the

6 landscape and paradigm for RAAS inhibition really

7 deserves a little further inspection.

8   I think as I look at the ACCHA (ph)

9 guidelines, there's two criteria that they use to

10 determine the level of recommendations for a

11 medication. The first is the robustness or the size

12 of the treatment effect. And the second is the

13 certainty surrounding that effect. And I think on

14 both counts we're seeing diminishing returns here. So

15 I think my concern is that when we look at the

16 totality of the evidence and we add in CHARM

17 preserved, I preserved, people who have normal,

18 healthy function, all these trials are negative. Add

19 that to PRoFESS, add that to TRANSCEND and so I think

20 it's certainly worth further discussion in terms of

21 where we go as a field. So that was my rationale.

22   DR. HARRINGTON: Ralph.

1   DR. D'AGOSTINO: I voted no on 6-A because I

2   thought the level of proof that was required for

3   approval was not met. I voted yes on 6-B because I

4   think that there is a need and this drug does appear

5   that it could possibly address it.

6   DR. HARRINGTON: Other comments from the

7   panel or questions from Drs. O'Neill, Stockbridge or

8   Temple? Any final words, Bob or Norm?

9   DR. TEMPLE: Well, I thought it was one of

10   the most detailed discussions -- I hope you all

11   enjoyed it -- of non-inferiority studies and the

12   difficulties. This is why it takes 60 pages to explain

13   it properly. And there's a lot of things, more than

14   usual, that don't have perfectly precise perfect

15   answers and calls for a lot of judgment, which makes

16   everybody nervous because it's not the kind of proof

17   positive that you'd like to have. I think we thought

18   it was a very good discussion.

19   I don't usually do this, but I want to

20   compliment the efforts of the company. They

21   didn't -- they weren't all successful, and that's

22   disappointing, of course. But it was a very ambitious

1   program and I'm sure a good commercial cause, but also

2   a good therapeutic cause. And I guess we all wish it

3   had been more unequivocally positive on some things so

4   that our job would be easier. But I think it was a

5   good effort.

6   DR. HARRINGTON: Yes, I'll echo that last

7   part, that unlike some of these meetings where you see

8   scanty data, we certainly had a lot of data. And I

9   thought it was well analyzed and well presented. So

10 again, my compliments.

11   Sanjay?

12   DR. KAUL: I'd like to echo Bob Temple's

13 comments. It was a humbling yet illuminating

14 experience for me. I've written a few papers on the

15 subject matter, and I do realize the challenges when

16 you're confronted with non-inferiority assessment.

17 And at least in my mind, I think we have shed light on

18 those issues and hopefully, we'll be able to move

19 forward. In that regard, the discussion has been very

20 enlightening for me.

21   DR. HARRINGTON: Yes, I don't think these

22 discussions are over at this advisory committee. But

1   thank you, everybody and --

2   Dr. Paganini and then I'll let Dr. Yusuf

3   have a word as well.

4   DR. PAGANINI: I just want to thank Norman

5   for putting me into the right perspective of the value

6   of my vote. That's all.

7   DR. HARRINGTON: Dr. Yusuf.

8   DR. YUSUF: I'm going to do something

9   unconventional, but I'd like to thank the FDA

10   statisticians who analyzed this very carefully. You

11   forced us to think, and as I thought, I learned. I

12   also want to thank the panelists. I think you gave

13   the whole thing a fair shake, and you landed where I

14   think most of us clinicians who are informed will

15   land. So I want to thank you for your careful effort.

16   Bob and Norm, the NI, the non-inferiority

17   area is so difficult, please consider in future not

18   just methods that will decrease confidence interval

19   and therefore double, quadruple your sample size. But

20   think of some means by which you use multiple

21   endpoints to give us greater confidence. So I think

22   we should go beyond the statistical boundary approach

1   alone but something more innovative. And I know in

2   September we have a meeting on it. I look forward to

3   it. Thank you.

4   DR. TEMPLE: And there will be a guidance

5   out in the not too distant future, we believe because

6   we promised it a long time ago, and you can send in

7   comments. Everybody can send in comments.

8   DR. HARRINGTON: Thank you, everybody.

9   Travel safely.

10   [Whereupon, at 4:17 p.m. the meeting was

11   adjourned.]

12

13

14

15

16

17

18

19

20

21

22